An Acyl Radical Cascade Model for the Total Synthesis of Lyconadin A

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AN ACYL RADICAL CASCADE MODEL FOR THE
TOTAL SYNTHESIS OF LYCONADIN A

by

Seth Wilson Grant

A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry and Biochemistry
Brigham Young University
August 2005
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ABSTRACT

AN ACYL RADICAL CASCADE MODEL FOR THE TOTAL SYNTHESIS OF LYCONADIN A

Seth Wilson Grant

Department of Chemistry and Biochemistry

Master of Science

Lyconadin A (1) is a structurally unique Lycopodium alkaloid with antitumor properties, isolated from the club moss Lycopodium complanatum. We are developing a synthetic route to 1 based on a novel 7-exo-trig/6-exo-trig acyl radical cascade cyclization. The synthesis of model acyl radical cascade precursor 23 will be presented. Key features of this synthesis include the suppression of competing elimination during the alkylation of a hindered phenethyl bromide and the use of a lactone as a precursor to a compound bearing two differentially protected primary alcohols. An account of our
studies on the model acyl radical cascade cyclization (23 → 24 above) will also be given, including a stereochemical analysis of the product. Our findings have been applied to develop a more detailed stereoselective synthetic plan for Lyconadin A (1).
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# TABLE OF CONTENTS

Table of Contents ........................................................................................................................................ vii  
List of Figures .............................................................................................................................................. ix  
List of Schemes ........................................................................................................................................... x  
List of Tables ............................................................................................................................................. xii  

Chapter 1. Introduction .................................................................................................................................. 1  

1.1 Lyconadin A ........................................................................................................................................... 1  
1.2 Lycopodium Alkaloids ........................................................................................................................... 1  
1.3 Synthetic Approach to Lyconadin A .......................................................................................................... 4  
1.4 Acyl Radicals ........................................................................................................................................... 7  
1.5 Acyl Radical Cascade Reactions ............................................................................................................. 15  
1.6 References ............................................................................................................................................. 18  

Chapter 2. Synthesis of the Radical Cascade Precursor .................................................................................. 23  

2.1 Synthesis of Bromide 55 ......................................................................................................................... 23  
2.2 Alkylations ............................................................................................................................................. 26  
2.3 Synthesis of the Phenyl Selenoester ......................................................................................................... 30  
2.4 References ............................................................................................................................................. 33  

Chapter 3. Model Acyl Radical Cascade Studies .......................................................................................... 35  

3.1 Conditions for the Acyl Radical Cascade ............................................................................................... 35  
3.2 Stereochemistry of the Acyl Radical Cascade .................................................................................... 37  
3.3 References ............................................................................................................................................. 40
Chapter 4. Future Work and Conclusions .................................................................41
  4.1 Stereochemical Issues of the Radical Cascade .................................................41
  4.2 Application of the Model Acyl Radical Cascade to Lyconadin A .................42
  4.3 Conclusion .......................................................................................................44
  4.4 References ......................................................................................................45

Chapter 5. Experimental and Spectroscopic Data ..................................................46
  5.1 General Methods ............................................................................................46
  5.2 Experimental Details .....................................................................................46
  5.3 References ......................................................................................................67
  5.4 Selected NMR Spectra .................................................................................68
LIST OF FIGURES

Chapter 1. Introduction

Figure 1. Lyconadin A (1) .................................................................1
Figure 2. Classes of Lycopodium Alkaloids ........................................2
Figure 3. Huperzine A (6) .................................................................3

Chapter 3. Model Acyl Radical Cascade Studies

Figure 1. Phenyl Selenoester syn-23 .................................................35
Figure 2. Conformations of 24 for NMR Analysis ...............................39

Chapter 4. Future Work and Conclusions

Figure 1. Model Acyl Radical Cascade Product (24) ..........................41
Figure 2. Stereochemistry Required for the Total Synthesis of Lyconadin A....42
Chapter 1. Introduction

Scheme 1. Proposed Biosynthesis of Lyconadin A .................................................4
Scheme 2. Retrosynthesis of Lyconadin A ..............................................................5
Scheme 3. Mechanism of the Proposed Acyl Radical Cascade .........................6
Scheme 4. Generation of Acyl Radicals .................................................................8
Scheme 5. Reactions of Acyl Radicals ..................................................................10
Scheme 6. Decarbonylation can Attenuate Yields ..................................................11
Scheme 7. The Exo/Endo Problem .........................................................................12
Scheme 8. 7-Exo Cyclizations of Acyl Radicals (Boger and Mathvink) ..............13
Scheme 9. 7-Exo Cyclizations of Acyl Radicals (Evans) .......................................14
Scheme 10. 7-Exo Cyclizations of Acyl Radicals (Bonjoch) .................................14
Scheme 11. 7-Exo Cyclizations of Acyl Radicals (Ryu) .......................................15
Scheme 12. Acyl Radical Cascade (Curran) ............................................................16
Scheme 13. Acyl Radical Cascade (Pattenden) .....................................................17
Scheme 14. Acyl Radical Cascade (Pattenden) .....................................................17
Scheme 15. Acyl Radical Cascade (Crich) ............................................................18

Chapter 2. Synthesis of the Radical Cascade Precursor

Scheme 1. Retrosynthetic Approach to Phenyl Selenoester 23 .........................23
Scheme 2. Synthesis of Mono-Protected Diols......................................................24
Scheme 3. Alkylation of β-Keto Ester 63 ..............................................................27
Scheme 4. Alkylation of β-Keto Ester 64 ..............................................................28

Scheme 5. Synthesis of diPMB-Dihydroxy Ketone 69 .........................................28

Scheme 6. Attempted Alkylation of Free β-Hydroxy Ester 70 .............................29

Scheme 7. DEADC Alkylation ..............................................................................30

Scheme 8. Preparation of Bis-Weinreb Amide 73 .................................................31

Scheme 9. Double Reduction/Wittig Approach to Diene Formation ....................32

Scheme 10. Oxidation and Phenylselenation .........................................................33

Chapter 3. Model Acyl Radical Cascade Studies

Scheme 1. Acyl Radical Cascade Cyclization of Phenyl Selenoester syn-23........37

Scheme 2. Proposed Stereochemistry of the Acyl Radical Cascade .....................38

Chapter 4. Future Work and Conclusions

Scheme 1. Suggested Methods for Epimerization of 24 ........................................43

Scheme 2. Modified Acyl Radical Cascade Approach to Lyconadin A ............44
LIST OF TABLES

Chapter 2. Synthesis of the Radical Cascade Precursor

Table 1. Bromination of Mono-Protected Diols 59a-c ........................................25
CHAPTER 1. INTRODUCTION

1.1 Lyconadin A

The alkoloid Lyconadin A (1, Figure 1) was recently isolated from the club moss *Lycopodium complanatum* and fully characterized by Kobayashi and co-workers.\(^1\) Its structure was determined by a combination of HRMS, IR, and 2-D NMR techniques. The novel bridged pentacyclic skeleton of Lyconadin A consists of an \(\alpha\)-pyridone ring, as well as one five-membered and three six-membered rings. It also contains six stereocenters. In addition to its novel architecture Lyconadin A also exhibits in vitro cytotoxicity against two cancer cell lines: murine lymphoma L1210 cells (IC\(_{50}\) = 0.46 \(\mu\)g/mL) and human epidermoid carcinoma KB cells (IC\(_{50}\) = 1.7 \(\mu\)g/mL).\(^1\) Despite its appealing structure and biological activity, to date Lyconadin A has not been synthesized, and only one possible approach to its synthesis has been reported.\(^2\)

![Figure 1. Lyconadin A (1)](image)

1.2 Lycopodium Alkaloids

Lyconadin A belongs to the lycopodium alkaloid family, a diverse group of natural products generally consisting of sixteen carbon and one or two nitrogen atoms, with various degrees of oxygenation. They are presumably derived from two 2-propylpiperidine subunits (thus the numbering in Figure 1). Ma and Gang recently
reviewed the chemical, pharmacological, and clinical research being performed on this family of alkaloids, and several previous reviews exist as well.\textsuperscript{4,5}

The lycopodium family is often divided into four classes based on their structural skeletons.\textsuperscript{3} These classes are the Lycodines, the Lycopodines, the Fawcettimines, and a Miscellaneous class. A typical example from each of these classes is shown in Figure 2 (Phlegmarine is the example from the miscellaneous class). Although the biosynthesis of the lycopodium alkaloids is not completely understood, it is thought that Phlegmarine (2), in which the two 2-propylpiperidine subunits are more obvious, is the common precursor to all classes of the Lycopodium alkaloids. Thus, bond formation between C-4 and C-13 of Phlegmarine yields the Lycodine skeleton (3). From Lycodine, disconnection of the C-1–N\textsubscript{α} bond, and reconnection of C-1 to N\textsubscript{β} gives the Lycopodine structure (4). From there, migration of C-4 from C-13 to C-12 reveals the Fawcettimine (5) skeleton.

Many members of the lycopodium alkaloid family are biologically active. For example, an exclusive feature of many compounds in the Lycodine subclass is their ability to inhibit acetylcholinesterase.\textsuperscript{6,7} Of these, Huperzine A (6, Figure 3) is the most potent.\textsuperscript{8,9} It has been shown that due to its strong inhibition of acetylcholinesterase it increases memory and learning efficiency in mammals,\textsuperscript{8,9} and shows promise in the treatment of Alzheimer’s disease and myasthenia gravis.\textsuperscript{10,11} Huperzine A and a Schiff
base derivative of Huperzine A named ZT-1 are currently in clinical trials for use as a
treatment for Alzheimer’s disease.\(^3\)

![Figure 3. Huperzine A (6)](image)

It is proposed that Lyconadin A, a member of the miscellaneous class (Figure 2)
and all other lycopodium alkaloids are derived biologically from two 2-propylpiperidine
moieties via Phlegmarine (2). The proposed biosynthesis\(^3\) of Lyconadin A is shown in
Scheme 1. Decarboxylation of L-lysine gives Cadaverine (7), which upon oxidation and
imine formation gives \(\Delta^1\)-Piperideine (8). Meanwhile, Malonyl-CoA (9) can undergo
self-condensation followed by decarboxylation to give 10 (\(X = \text{OH or SCoA}\)). Addition
of this acetone derivative to 8, again followed by decarboxylation, gives 4PAA or
4PAACoA (11 or 12), which is hydrolyzed (if necessary) and yet again decarboxylated to
give Pelletierine (13). Condensation of 11 or 12 with Pelletierine, decarboxylation, and
ring closure affords Phlegmarine (2), the intermediate thought to be the diverging point
for all Lycopodium alkaloids. From there, epimerization of C-13 and oxidation of the A
ring to an \(\alpha\)-pyridone (14), followed by C-6–N\(\beta\) and C-4–C-10 bond formation gives
Lyconadin A, 1. This proposed biosynthesis is supported up through Phlegmarine (2) by
feeder studies.\(^3\)
1.3 Synthetic Approach to Lyconadin A

Any total synthesis of 1 would be faced with the task of constructing the pentacyclic ring system. Our approach to this challenge is shown in retrosynthetic form in Scheme 2. We propose that a one-pot double-intramolecular-reductive amination could form two of the C–N bonds simultaneously. In the reverse direction, protection and disconnection of the C-13–N and C-6–N bonds reveals 15, which consists of a bicyclo[5.4.0]undecane ring system, fused to a pyridone. We believe this ring system can be achieved via a tandem 7-exo-trig/6-exo-trig radical cascade reaction of the acyl radical generated from phenyl selenoester 16. This reaction represents a novel radical cascade system. Should this proposed reaction not give the appropriate stereochemistry, modifications to 16 could allow for stereoselective installation of the requisite stereocenters. Compound 16 in turn could be formed in a convergent manner from the
stereoselective addition of the cuprate derived from bromide 18 with the known\textsuperscript{12} chiral epoxy alcohol 17, according to Hamada’s procedure,\textsuperscript{13} followed by standard transformations. A close analogue of 18 would be readily available from compound 19, methyl propiolate, and ammonia via Kozikowski’s pyridone synthesis.\textsuperscript{14} \(\alpha\)-Keto ester 19 could be prepared by the Horner–Emmons reaction of known\textsuperscript{15} phosphonate 20 with aldehyde 21, which should in turn be available from triol 22 via an enzymatic asymmetrization.\textsuperscript{16}

\[
\begin{align*}
\text{Scheme 2. Retrosynthesis of Lyconadin A}
\end{align*}
\]

The key step in our proposed synthesis of Lyconadin A is the acyl radical cascade cyclization (16 \(\rightarrow\) 15, Scheme 2). This proposed novel radical cascade reaction represents a significant risk at such a late stage in the total synthesis. Consequently, it would be wise to evaluate the feasibility and stereoselectivity of this reaction on a simpler substrate, such as phenyl selenoester 23 (Scheme 3), prior to applying it in the total synthesis. This phenyl selenoester will serve as an adequate model for the desired radical
cascade cyclization step because it contains the key components of 16 in the proper relative positions, and should be easier to prepare. Scheme 3 shows the mechanism we expect to be operative in the model cascade reaction. Treatment of phenyl selenoester 23 with either stannyl or silyl radicals should generate an acyl radical. We anticipate that this acyl radical will add in a 7-exo fashion across the first alkene, and that the newly generated primary radical will subsequently add to the second alkene in a 6-exo manner. Propagation of the chain should provide 24, which, to the best of our knowledge, will demonstrate the first application of an acyl radical cascade reaction to prepare the bicyclo[5.4.0]undecane ring system. The goal of my project is to synthesize phenyl selenoester 23 and use it to explore this proposed acyl radical cascade. Based on the regio- and stereochemical results of the model study, we will develop a more detailed synthetic route to Lyconadin A.

Upon inspection of compound 23 one will immediately note the absence of defined stereochemistry. We hope to investigate the possibility of substrate control on the stereoselectivity of the two new stereocenters formed in the radical cascade. To fully
explore this aspect of the reaction we need both diastereomers of phenyl selenoester 23. Thus, its synthesis should allow for formation and separation of the two diastereomers as racemic mixtures. A thorough investigation of this novel acyl radical cascade on each diastereomer will provide not only confirmation of the feasibility of the proposed radical cascade, but will also supply valuable information about the degree of stereoselectivity that can be expected when this reaction is applied in the total synthesis. Should the stereoselectivity be poor, we will attempt to incorporate appropriate functionality into compound 16 (Scheme 2) during the total synthesis that will allow us to define the appropriate stereochemistry following the radical cascade cyclization. An example of such a modification is the replacement of the first alkene with an alkyne, thus generating an enone, which could subsequently be reduced stereoselectively.

1.4 Acyl Radicals

The chemistry of acyl radicals has been thoroughly reviewed by Chatgilialoglu, Crich, Komatsu, and Ryu and the reader is referred to their article for additional details and a comprehensive list of references. An acyl radical is any compound of the general formula RC(O)•, in which an unpaired electron occupies a sigma orbital on the $sp^2$-hybridized carbonyl carbon. This orbital is orthogonal to the $\pi$ bond and thus the unpaired electron is not delocalized, although it is possible that it mixes to some extent with an electron pair of the oxygen. These structural features give the carbonyl carbon a bent geometry.

Acyl radicals can be generated in three ways (Scheme 4). The most common method is the homolytic cleavage of the carbonyl C–X bond (method a). This method is
known where $X$ is a H, Cl, Br, S, Se, Te, or Co atom. Historically, homolysis of aldehydes and acyl chlorides was the primary approach to acyl radical generation by this method, although neither of these processes is known to be highly efficient. However, aldehydes can form acyl radicals when treated with peroxides, and the efficiency is increased when the reaction is catalyzed by thiols.\(^{18,19}\) Acyl chlorides can also form acyl radicals when treated with a radical initiator and a chain carrier, although the stannane-mediated reactions face significant complications. A more successful approach employs $(\text{TMS})_3\text{SiH}$ as the chain carrier.\(^{20}\) Acyl chlorides also form acyl radicals when treated with Sm(II) complexes,\(^{21,22}\) although the acyl radical or the resulting products often undergo further reduction by the samarium. Aryl thioesters (RCOSAr) generate acyl radicals upon photolysis or vigorous thermolysis,\(^ {23-25}\) although they are unreactive\(^ {26}\) toward the tributylstannyl radical, which limits their synthetic applicability. Acyl tellurides\(^ {27}\) and acylcobalt(III) complexes\(^ {28}\) have been shown to generate acyl radicals upon irradiation, although they have not found widespread application.

\[
\begin{align*}
\text{RX} + \text{CO} & \quad \rightarrow \quad \text{RX} + \text{CO} \\
\text{RX} + \text{CO} & \quad \rightarrow \quad \text{RX} + \text{CO} \\
\text{RX} + \text{CO} & \quad \rightarrow \quad \text{RX} + \text{CO}
\end{align*}
\]

\textbf{Scheme 4. Generation of Acyl Radicals}

The most common substrate currently used to generate acyl radicals in organic synthesis is the phenyl selenoester (RCOSePh), originally developed by Graf and co-workers,\(^ {29,30}\) who demonstrated its use as a decarbonylation precursor. Phenyl selenoesters are the preferred acyl radical precursors because they do not face the complications that acyl chlorides do, such as isolation, purification by silica gel
chromatography, and over-reduction. In addition, unlike aldehydes and aryl thioesters, they react readily with either stannyl or tris(trimethylsilyl)silyl radicals.\textsuperscript{31} They can be prepared from the corresponding acyl chlorides using benzeneselenol\textsuperscript{29,30,32,33} or diphenyl diselenide\textsuperscript{34,35} (PhSeSePh). More conveniently however, phenyl selenoesters can also be prepared from carboxylic acids by employing $N$-phenylselenophthalimide,\textsuperscript{36,37} phenylselenyl chloride,\textsuperscript{38} or diphenyl diselenide.\textsuperscript{39} Methyl selenoesters are also known acyl radical precursors; their preparation from $O$-alkyl esters using dimethylaluminum methaneselenolate\textsuperscript{40} and use as acyl radical precursors\textsuperscript{41} is documented.

The generation of acyl radicals by carbonylation of alkyl radicals (method b, Scheme 4) has been reviewed by Ryu and Sonoda.\textsuperscript{42} Alkyl or aryl bromides, iodides, or selenides are used to generate an alkyl or aryl radical, which then adds to CO. The largest drawback to this method is that it requires a special apparatus for increased pressures (80–90 atm of CO is common). Although this reaction can be used to append a formyl group onto an alkyl or aryl backbone, it is most useful when the intermediate acyl radical reacts further in either an inter- or intramolecular sense.

The third method for generation of acyl radicals is the photochemical cleavage of C–C bonds of ketones, known as the Norrish type I reaction (method c, Scheme 4). Irradiation of a ketone excites it ($n \rightarrow \pi^*$) into the singlet state, which rapidly undergoes intersystem crossing to the triplet excited state, from which homolytic $\alpha$-cleavage can occur.\textsuperscript{43} The weaker of the two C–C bonds is cleaved, generating the most stable alkyl radical. The reaction is facilitated by ring strain in the case of cycloalkanones. One advantage of this reaction is that it cleanly generates acyl radicals for use in spectroscopic studies.\textsuperscript{17}
Acyl radicals are considered nucleophilic radicals because they add more efficiently to electrophilic species. Regardless of the fashion in which they are generated, acyl radicals can undergo several types of reactions, including decarbonylation, homolytic substitution, additions to π bonds, and oxidation/reduction chemistry. These reactions are summarized in Scheme 5, and will be discussed below. However, oxidation and reduction reactions will not be discussed here because the acyl radical is typically just an intermediate in the reaction, and this type of reaction is not pertinent to the work that will be presented in this thesis.

![Scheme 5. Reactions of Acyl Radicals](image)

Decarbonylation is the reversible loss of carbon monoxide from an acyl radical to form an alkyl radical. The rate of decarbonylation depends on the nature of the alkyl or aryl group and reflects the stability of the alkyl radical formed; the relative rates\(^{17}\) are

\[
\text{ArCH}_2\text{C(O)•} > \text{R}_3\text{CC(O)•} > \text{R}_2\text{CHC(O)•} > \text{RCH}_2\text{C(O)•} > \text{CH}_3\text{C(O)•} >> \text{ArC(O)•.}
\]

Although decarbonylation can be a useful tool for removal of an unnecessary carbonyl group, more frequently it is an undesired side reaction. For example, Boger and Mathvink reported\(^{44}\) a series of intramolecular acyl radical addition reactions in which the yield of cyclized product uniformly decreased as substitution at the α-carbon incrementally increased (Scheme 6). However, decarbonylation is attenuated at lower
temperatures. Consequently, an O₂/Et₃B system has been developed for radical initiation at room temperature and lower. In addition, since this reaction is reversible, simply running the reaction under a moderate pressure of CO can bias the equilibrium toward the acyl radical.

![Scheme 6. Decarbonylation can Attenuate Yields](image)

A second type of reaction that acyl radicals can undergo is homolytic substitution (Scheme 5). This reactivity of acyl radicals has been exploited to convert aldehydes directly into acyl chlorides, bromides, and iodides, most of which were trapped in situ by alcohols or amines to form the corresponding esters or amides. Perhaps the most efficient of these transformations is the AIBN-initiated conversion of aldehydes into acyl bromides using N-bromosuccinimide. Acyl radicals can also substitute at sulfur, selenium, and tellurium atoms, generating acyl sulfides, selenides, and tellurides respectively. However, these reactions are less useful because they require an acyl radical to form substrates that are most commonly used as acyl radical precursors.

The most synthetically useful reaction of acyl radicals is their addition to π bonds, most commonly to an alkene. Because of their nucleophilic nature, acyl radicals add more efficiently to electron-poor alkenes such as α,β-unsaturated carbonyl compounds. (This type of reaction creates a 1,4-dicarbonyl compound, which is complementary to the formation of 1,5-dicarbonyl compounds by means of the Michael addition of an enolate in traditional ionic chemistry.) Acyl radicals add to alkenes in both inter- and
intramolecular reactions.\textsuperscript{44} In fact, macrocyclization has been performed by intramolecular addition of acyl radicals to enones and acrylates.\textsuperscript{51,52} One issue that has complicated the synthetic applications of acyl radical additions to alkenes is the occasionally poor \textit{exo/endo} selectivity. This issue is thoroughly discussed in the review by Chatgilialoglu et al.\textsuperscript{17} They conclude that “acyl radical cyclizations are not reversible on any kinetically significant time scale and that \textit{endo} mode products can arise both by Beckwith/Dowd-type rearrangement of \textit{exo} cyclized radicals or directly from the acyl radical depending on the substitution patterns employed.” This conclusion is depicted in Scheme 7. Despite this irregular complication, the addition of acyl radicals to alkenes has found application in total synthesis endeavors.\textsuperscript{53}

![Scheme 7. The Exo/Endo Problem](image)

Of particular interest in our case is the ability of acyl radicals to add to $\pi$ bonds in a 7-\textit{exo} fashion. Although there are not many examples of this mode of acyl radical addition, it is a known process that can proceed in good yield and afford good diastereoselectivity given the proper arrangement of substituents. To the best of our knowledge the work presented in this section is a summary of all documented examples of this type of acyl radical cyclization.

The first examples of acyl radicals undergoing 7-\textit{exo}-trig cyclizations were reported by Boger and Mathvink\textsuperscript{26,44} and are shown in Scheme 8. As with most other
examples, the acyl radicals were formed from a corresponding selenoester. Conversion of 27a-b to 28a-b shows the improved efficiency of acyl radical additions to electron-deficient alkenes relative to non-activated alkenes. In fact, the formation of 28a is the only known example of an acyl radical adding to a non-activated alkene in a 7-exo fashion.

![Scheme 8. 7-Exo Cyclizations of Acyl Radicals (Boger and Mathvink)](image)

Andrew Evans has also contributed significantly to the field of acyl radical addition reactions. He and his co-workers have performed the 7-exo cyclizations shown in Scheme 9. The first and second examples demonstrate the intramolecular addition of acyl radicals to vinylogous sulphonates and carbonates respectively, for the diastereoselective formation of tetrahydrooxepines. Of note, the major isomer of 32 is the product derived from a chair-like transition state in which both substituents occupy pseudo-equatorial positions.
Scheme 9. 7-Exo Cyclizations of Acyl Radicals (Evans)

Scheme 10 shows an example of a 7-exo cyclization of an acyl radical, in which Bonjoch and co-workers describe the decarbonylation of α-amino acyl radicals but not of the corresponding β-amino acyl radicals. This is the only example of a 7-exo acyl radical addition forming a bridged bicyclic compound.

Scheme 10. 7-Exo Cyclizations of Acyl Radicals (Bonjoch)

Ryu and co-workers have demonstrated the 7-exo addition of acyl radicals to the nitrogen atom of imines (Scheme 11), in which the acyl radicals were generated by carbonylation of vinyl radicals. The Z-selectivity of 40 was attributed to a weak electronic interaction between the carbonyl oxygen and the tin atom, whereas the
contrasting *E*-selectivity of 41 was attributed to steric repulsion. They were able to demonstrate this methodology over a broad range of substrates for the preparation of 4- to 9-membered *α*-methylene lactams.

![Scheme 11. 7-Exo Cyclizations of Acyl Radicals (Ryu)](image)

1.5 Acyl Radical Cascade Reactions

Acyl radicals have also been employed in radical cascade reactions, in which multiple C–C bonds and more than one ring are formed in a single chemical transformation. This class of reactions has been referred to as cascade, domino, or tandem reactions. McCarroll and Walton have written a review on radical cascades in which they explain the relationship between the acyclic precursors and the complex polycyclic products. “The structure of the precursor molecule(s) must be carefully ‘programmed’ to enable a complex, scripted, reaction coordinate to be followed, predictably bringing about a drastic configurational change, and ending in the target molecular design.” They refer to the precursor molecules as “chemical algorithms”. They also developed a nomenclature system to describe radical cascade reactions. According to their system, our proposed cascade would be a $C^7xC^{6x}$ process. To the best of our knowledge this is a novel radical cascade system.

Chatgilialoglu et al. included a section on tandem reactions in their review of acyl radicals. Herein will be presented only a few interesting examples. The first (Scheme
12) shows one of several radical cascade approaches to the angular triquinane ring system. Treatment of 5,5-disubstituted cyclopentadiene 42 with stannyl radicals generated an acyl radical which added across an alkene in a 5-\textit{exo-trig} fashion to generate the allylic radical 43. A second 5-\textit{exo-trig} cyclization afforded the diastereomers 44 and 45 along with the prematurely reduced bicyclic compound 46 in a 1:5:2 ratio. Of note, the “movement” of the radical center in intermediate 43 due to its allylic nature is formally considered a 1,3-transposition.

![Scheme 12. Acyl Radical Cascade (Curran)](image)

Another impressive example of the use of an acyl radical in a cascade cyclization is the transformation\(^\text{63}\) of phenyl selenoester 47 into the steroidal tetracyclic ketone 48 (Scheme 13). The initially formed acyl radical undergoes four consecutive 6-\textit{endo-trig} cyclizations, each of which is completely diastereoselective. Unfortunately the propagation step was not, and the D ring was formed as a mixture of methyl epimers. This example shows the potential of radical cascades for the diastereoselective formation of polycyclic compounds.
Pattenden has reported another remarkable example of an acyl radical cascade for the formation of steroid ring systems.\textsuperscript{64} This cascade proceeds from phenyl selenoester 49 (Scheme 14) via two consecutive 6-\textit{endo}-trig cyclizations, a cyclopropylcarbinyl ring opening (formally a 1,4-transposition), a 9-\textit{endo}-trig macrocyclization, and finally a transannular 5-\textit{exo}-trig addition. This cascade gave the unusual \textit{cis}, \textit{anti}, \textit{cis}, \textit{anti}, \textit{cis} diastereomer 50 as the major product.

The last example of note involves a 7-\textit{endo}-trig/5-\textit{exo}-dig cascade, which was favored over the competing initial 6-\textit{exo}-trig cyclization.\textsuperscript{65,66} Acyl radical generation from phenyl selenoester 51 generated the bicyclo[5.3.0]decane ring system of 52 in modest yield and as a mixture of four diastereomers (Scheme 15). Presumably the 1,3-dioxolane prevents the substrate from adopting a conformation favorable for a 6-\textit{exo} approach of the acyl radical.
Scheme 15. Acyl Radical Cascade (Crich)

\[
\begin{align*}
\text{Bu}_3\text{SnH, AIBN} & \quad \text{C}_6\text{H}_6, \text{reflux} \\
51 & \quad 45\%
\end{align*}
\]

1.6 References


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    5466.
53. For representative examples see (a) Barton, D. H. R.; Clive, D. L. J.; Magnus, P. D.;
    Shishido, K. Tetrahedron Lett. 1998, 39, 5803–5806. (c) Astley, M. P.; Pattenden,
    11010.
CHAPTER 2. SYNTHESIS OF THE RADICAL CASCADE PRECURSOR

In order to explore the proposed novel acyl radical cascade cyclization we began by developing a synthesis of the model radical cascade precursor. A brief retrosynthetic analysis of phenyl selenoester 23 is shown in general form in Scheme 1. In the reverse direction from 23, standard transformations reveal compound 53. The key disconnection in the retrosynthetic analysis is an alkylation reaction of an appropriately functionalized ketone (54) with bromide 55 to install the carbon framework of 53. The R-groups in compounds 54 and 53 must provide functionality that can be converted into alkenes. We envisioned that bromide 55 could be derived from known¹ lactone 56 through the intermediacy of a differentially protected diol in which each alcohol group is primary.

Scheme 1. Retrosynthetic Approach to Phenyl Selenoester 23

2.1 Synthesis of Bromide 55

In the forward direction, lactone 56 was prepared according to Kim’s method² and subjected to basic hydrolysis. Both the alcohol and acid functionalities of the resulting hydroxy acid were protected with PMB–Cl to give 57 (Scheme 2). It should be noted that limited attempts to use other protecting groups such as TBS resulted in reformation
of the lactone, which was a standard byproduct in the bisprotection reaction. LAH reduction of 57, followed by protection with the appropriate silyl chloride provided a series of differentially protected diols (58a-c). The PMB group was then removed by oxidative cleavage using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford the parallel set of mono-protected diols 59a-c.

\[ \text{Scheme 2. Synthesis of Mono-Protected Diols} \]

Initially, only mono-tert-butyldimethylsilyl diol 59a was prepared. However, when it was subjected to a Mitsunobu-type bromination, the result was an approximately 2:1 mixture of bromo alcohol 61 and dibromide 62 (Table 1). A search of the literature revealed that the Mitsunobu bromination procedure is an efficient method for the direct conversion of alkyl silyl ethers to alkyl bromides, in which more bulky silyl ethers require longer reaction times. Although the mechanism of this transformation was not proposed in the cited communication, it can be inferred from the presence of bromo alcohol 61 in the product mixture that under Mitsunobu conditions the silyl ether is first cleaved, and that the resulting alcohol is subsequently converted into the bromide. Accordingly, we next attempted to use this transformation to our advantage by switching the TBS and PMB protecting groups, which would eliminate a deprotection step. However, as mentioned above, bisprotection of the hydroxy acid resulting from the
Saponification of 56 with TBS–Cl resulted in reformation of the lactone, even when NaH was employed as the base.

Consequently, we began to screen the Mitsunobu-type brominations of the more bulky mono-tert-butyldiphenylsilyl and triisopropylsilyl diols 59b and 59c, hoping that the increased bulk of the silyl ethers would retard the rate of the undesired bromination. The reaction with 59b gave an almost 1:1 mixture of the inseparable regioisomeric bromides 55b and 60b (Table 1), the latter presumably arising from silyl migration.4 When the reaction conditions were applied to mono-TIPS diol 59c some of the desired product formed and less silyl migration occurred (Table 1), but a significant amount of TIPS-deprotection was observed, giving an approximately 1:<0.5:1 mixture of compounds.

**Table 1. Bromination of Mono-Protected Diols 59a-c**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Ratio of 55:60:61:62</th>
<th>Combined Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>59a</td>
<td>A</td>
<td>0:0:2:1</td>
<td>94%</td>
</tr>
<tr>
<td>59b</td>
<td>A</td>
<td>1:1:0:0</td>
<td>63%</td>
</tr>
<tr>
<td>59c</td>
<td>A</td>
<td>1:&lt;0.5:1:0</td>
<td>71%</td>
</tr>
<tr>
<td>59c</td>
<td>B</td>
<td>1:0:0:0</td>
<td>93%</td>
</tr>
<tr>
<td>59b</td>
<td>B</td>
<td>1:0:0:0</td>
<td>77%</td>
</tr>
<tr>
<td><strong>59a</strong></td>
<td><strong>B</strong></td>
<td><strong>1:0:0:0</strong></td>
<td><strong>99%</strong></td>
</tr>
</tbody>
</table>
Based on the above results it was apparent that the Mitsunobu-type bromination was not going to lead to any synthetically useful results in our case, and that other reaction conditions should be explored. We next attempted the desired transformation by means of a one-pot mesylation/bromination. Treatment of 59a-c with MsCl, Et₃N, and LiBr in THF⁵ afforded the desired bromides 55a-c, with the only detectable byproduct being the corresponding mesylate, which could be completely converted to the bromide after extended reaction times (4–6 days). Employing this procedure, bromides 55a-c were prepared in high yields, often with no need for chromatography (Table 1). A study of the brominations run in parallel revealed that 59a (TBS ether) reacted the fastest, 59b (TBDPS ether) was a close second, and 59c (TIPS ether) was significantly slower. Since the bromination was faster and the TBS group is easier to remove, we chose 55a as the bromide that would be carried on to further reactions.

The sequence of reactions shown in Scheme 2 and Table 1 was amenable to a multigram preparation of bromide 55a. The six-step method was used to prepare 6.2 g of the bromide, with an overall yield of 35% from the known lactone 56, an average yield of 84% per step.

2.2 Alkylations

With bromide 55a in hand we next turned our attention to the key alkylation step and selection of an appropriate ketone. The appropriate ketone would require β,γ-unsaturation on each side, or some functionality that could easily be converted into the desired 1,6-diene. We initially attempted the alkylation with β-keto ester 63 (Scheme 3), which was prepared according to a literature procedure.⁶ Two sets of conditions were
applied for this alkylation reaction. Neither of them was successful in delivering the desired product, and in each case the β-keto ester was consumed. We believe that the β,γ-enone moiety of 63 was isomerizing to the more stable α,β-enone, followed by polymerization via Michael addition.

Since we could find no literature precedent for alkylation of a β-keto ester containing a β,γ-enone moiety we next attempted the alkylation with β-keto ester 64 (Scheme 4), an analogue of 63 in which the alkene is masked as a protected alcohol (deprotection, oxidation, and Wittig reactions would unmask the alkene). Again, 64 was synthesized according to literature procedures. For this alkylation we employed the conditions developed by Johnson and co-workers in which the enolate is formed in THF using NaH as the base, the bromide is added, most of the THF is removed in vacuo and replaced with the more polar solvent acetonitrile, and NaI is added as a nucleophilic catalyst. The reaction is then heated (60 °C) for an extended period of time. Following this procedure, we were able to isolate the desired alkylation product 65 (Scheme 4) in yields of up to 47%. The remainder of bromide 55a was typically converted into its iodide and styrene derivatives. However, the yields of the desired product were modest at best, and they varied significantly (15–47%). In addition, the reactions subsequent to the alkylation proved problematic, so ultimately we chose another approach to the desired diene.
After making limited progress on the reactions following the alkylation of 64 we recognized the possibility of employing a symmetrical ketone in the alkylation step. Initially we focused on the synthesis and alkylation of a bisprotected β,β'-dihydroxy ketone. We began by protecting the ketone of diethyl acetone-1,3-dicarboxylate (DEADC, 66) as the 1,3-dioxolane to give 67 (Scheme 5). Reduction of the esters and protection of both free alcohols as PMB ethers afforded 68. Acid hydrolysis of the acetal, which surprisingly also partially cleaved the PMB ethers, gave the symmetrical ketone 69. When ketone 69 was subjected to low-temperature alkylation conditions (LDA in THF, –78 ºC) with bromide 55a, and the reaction allowed to warm to room temperature overnight, 55a was recovered in a near quantitative amount. In addition, PMB–OH was isolated (62% yield based on two equivalents), and following work-up a polymeric film formed. Obviously the enolate was undergoing E1cb elimination of the alkoxide of PMB–OH, and the newly generated enone was subsequently polymerizing. This is the result that we should have expected based on the substrate.
Following the unsuccessful alkylation employing a protected β-hydroxy ketone, a literature search revealed that free β-hydroxy esters have been successfully used in alkylation reactions. Accordingly, reduction of DEADC (66) with NaBH$_4$ gave β-hydroxy ester 70, with no need for purification. A single attempt at a low-temperature alkylation (2 eq. LDA) of 70 with bromide 55a resulted in the disappearance of 70 and near complete conversion of the bromide into the corresponding styrene 71 (Scheme 6). Presumably the alkoxide of 70 promoted the elimination of bromide 55a rather than its alkylation.

Eventually we realized that DEADC (66) itself is a symmetrical β-keto ester, and has potential to be alkylated with bromide 55a. After a failed attempt at performing this alkylation using NaOEt as the base in refluxing EtOH (complete conversion of the bromide into styrene 71), we applied Johnson’s alkylation conditions that were previously successful in the alkylation of β-keto ester 64 (see Scheme 4). We again found these conditions to be successful (Scheme 7), and were able to isolate compound 72 in a respectable yield of 41%. Upon scaling to 500 mg of the bromide, increasing the number of equivalents of DEADC to four, adding the bromide after switching solvents, and running the reaction at a higher concentration, the yield improved to a very satisfying 84%. Apart from improved yields, other advantages of this alkylation include the commercial availability of DEADC and the possibility of converting both esters of 72 into alkenes simultaneously. We hoped this would simplify the synthesis of phenyl
selenoester 23. It should be noted that this alkylation reaction was also amenable to scale-up; when the reaction was performed on 4.7 g of the bromide the yield was maintained at a healthy 73%.

![Scheme 7. DEADC Alkylation](image)

2.3 Synthesis of the Phenyl Selenoester

With the framework of phenyl selenoester 23 in place, functional group manipulations were to provide the desired radical cascade precursor. We expected that both esters of 72 could be converted into alkenes simultaneously through the intermediacy of a dialdehyde. We began by reducing the ketone of 72 with NaBH₄. The alcohol was then protected as a TBS ether, and the esters were both converted into Weinreb amides¹¹ in good yield to give bis-Weinreb amide 73 (Scheme 8). The reduction step generated a second stereocenter, and NMR analysis following TBS protection of the alcohol indicated a 2:1 mixture of the two diastereomers. Based on the reduction of a similar substrate reported in the literature¹² employing nearly identical conditions, we have tentatively assigned the relative stereochemistry of the major diastereomer as syn. Although the mixture of diastereomers was carried on, as we progressed through the remainder of the synthesis the minor diastereomer (the anti diastereomer) was purified out.
Initial attempts to reduce both Weinreb amides of 73 to aldehydes using DIBAL gave inconsistent mixtures of products that still exhibited some Weinreb amide signals in the crude NMR. In order to explore this reaction, 80 mg of bis-Weinreb amide 73 was subjected to DIBAL reduction at –78 °C, and every two hours a sample was removed, quenched, and analyzed by NMR. After the first two hours of reaction the NMR showed one set of Weinreb amide signals and an aldehyde signal corresponding to one hydrogen. In subsequent NMR’s the relative integration of the aldehyde signal slowly decreased and the Weinreb amide signals remained unchanged. We concluded that the less hindered Weinreb amide was being reduced to an alcohol prior to reduction of the more hindered Weinreb amide to the aldehyde. This is likely due to a coordination between the tetrahedral aluminum complex of the first reduced Weinreb amide and the unreduced second Weinreb amide. This complex would prevent another molecule of DIBAL from coordinating with the more hindered Weinreb amide, a necessary first step for the desired second reduction to occur. To circumvent this problem we performed the reduction/Wittig sequence in a stepwise fashion. As shown in Scheme 9, DIBAL reduction of 73 for only two hours, followed by a Wittig reaction with methyltriphenyl-phosphonium bromide, afforded alkene 74. At this point any remaining anti diastereomer was separable. Repeating the procedure installed the requisite 1,6-diene (75). As evidenced by the modest yields, this four-step sequence has yet to be fully optimized.
Highly selective cleavage of the primary TBS ether of 75 in the presence of the secondary TBS ether with (1S)-(+-)(10)-camphorsulfonic acid (CSA) then gave benzyl alcohol 76.

![Scheme 9. Double Reduction/Wittig Approach to Diene Formation](image)

The completion of the synthesis of phenyl selenoester 23 was accomplished by successive Swern and sodium chlorite oxidations, followed by phenylselenation (Scheme 10). As discussed in chapter 1, phenyl selenoesters can be prepared from the appropriate carboxylic acids or acyl chlorides using a variety of conditions. We initially attempted the phenylselenation employing Grieco’s conditions\(^\text{13}\) of N-phenylselenophthalimide and Bu₃P in CH₂Cl₂ (3a, Scheme 10). Although these conditions did generate phenyl selenoester 23 in low yield, compound 77, the product of phthalimide substitution, was the major product. (This type of byproduct was not mentioned in Grieco’s communication.) The yield of phenyl selenoester 23 was improved to 87% over the last three steps by switching the source of the phenylseleno group to diphenyl diselenide\(^\text{14}\) (3b, Scheme 10).
To summarize, we have successfully developed a synthesis of model phenyl selenoester syn-23. The synthesis is eighteen steps from known lactone 56 (nineteen steps from a commercially available compound), and has been achieved in an overall yield of 4.1%. The highlights of this synthesis include the use of a lactone as a precursor to a differentially protected diol in which each alcohol is primary, an alkylation of a phenethyl bromide with suppression of the corresponding facile elimination, and a stepwise installment of the two alkenes required to model the proposed acyl radical cascade. This last feature will be beneficial if we have a need to modify one of the alkenes (for example, replace it with an alkyne). An additional benefit of the synthesis is the ability to selectively choose the diastereomer. Although we have not yet explored this, the abundance of protocols for reduction of a ketone would likely provide a way to selectively prepare the anti diastereomer.

2.4 References


CHAPTER 3. MODEL ACYL RADICAL CASCADE STUDIES

With an adequate synthesis of phenyl selenoester 23 (Figure 1) developed, we next began to study the acyl radical cascade cyclization. This reaction, regardless of the conditions employed, faces several complications. First, when the acyl radical is generated, the loss of the phenylseleno group reduces the molecular weight by about one-third. Therefore experimentation on small scales is complicated by a significant reduction in mass. Second, because there are two radical intermediates along the desired pathway, premature reduction could generate two undesired products (ignoring possible stereoisomers). Other types of radical reactions such as hydrogen atom transfer could lead to additional undesired products. Third, if the cascade does proceed as we predict, two new stereocenters would be generated, allowing for the possible formation of up to four diastereomers of the desired product (assuming that the starting material is a single diastereomer to begin with).

![Figure 1. Phenyl Selenoester syn-23](image)

3.1 Conditions for the Acyl Radical Cascade

We expected that the initial 7-exo-trig cyclization would be the slow step of the intramolecular cascade. Accordingly we began our studies by attempting the cascade cyclization employing conditions that Boger and Mathvink developed\(^1\) for a 7-exo-trig cyclization similar to our system (see 27a → 28a, Scheme 8, Chapter 1). Their conditions called for radical initiation by 2,2'-azobisisobutyronitrile (AIBN) at elevated...
temperatures (refluxing benzene), and for chain propagation by Bu$_3$SnH. When we applied these conditions to the model system a very complex reaction mixture was obtained, with the only detectable product being the aldehyde corresponding to reduction of the acyl radical generated from phenyl selenoester 23.

Because the acyl radical was being reduced prematurely, we thought that a poorer chain propagator such as tris(trimethylsilyl)silane$^{2,3}$ would increase the lifetime of the radical intermediates, hopefully allowing for the desired intramolecular reactions to occur. Consequently we next employed conditions similar to those used by Evans and co-workers$^4$ for 7-exo-trig acyl radical cyclizations (see Scheme 9, Chapter 1), in which initiation occurs through the action of O$_2$ on Et$_3$B and (TMS)$_3$SiH is used as the chain carrier. As mentioned in Chapter 1, these conditions are known to generate radicals at or below room temperature.$^5$ In our case, these conditions generated the acyl radical of phenyl selenoester syn-23 at room temperature and promoted the radical cascade as proposed! This is evidenced by the lack of aldehydic or olefinic protons in the NMR, which precludes premature reduction or H-transfer reactions. Other modes of cyclization (for example 8-endo-trig/5-exo-trig) are unlikely based on their slower rates relative to 7-exo-trig cyclizations.$^{1,3}$ In addition, NMR analysis does not support the formation of any alternative cascade cyclization products. Thus, the bicyclo[5.4.0]undecane ring system of compound 24 was successfully installed (Scheme 1) in a very high yield of 93%. The reaction also appears to be highly diastereoselective as we have only been able to isolate a single diastereomer. To the best of our knowledge, this is the first reported example of an acyl radical cascade in which the first cyclization is in the 7-exo mode.
3.2 Stereochemistry of the Acyl Radical Cascade

With the successful acyl radical cascade completed, our next goal was to determine the relative stereochemistry of the major diastereomer. We propose that the major diastereomer will be the product in which the most possible groups are in equatorial or pseudo-equatorial positions in the transition states of each cyclization. Evans and co-workers have described similar selectivities in 7-\textit{exo-trig} acyl radical cyclizations.\textsuperscript{6,7} According to this model, acyl radical 78 (Scheme 2) would close on the first alkene in a 7-\textit{exo} fashion, such that both alkyl substituents occupy pseudo-equatorial positions in the transition state. This would generate the \textit{trans} ring fusion of primary radical 79. The transition state of the second cyclization would also adopt a chair-like conformation in which the \textit{exo} methylene group occupies an equatorial position. This would provide primary radical 80 with the stereochemistry shown. The TBS ether must occupy an axial position in the transition state between 79 and 80 because of the \textit{syn} stereochemistry of 23, and would reinforce the preference for the methylene group to be in an equatorial position in order to avoid highly energetic 1,3-diaxial interactions. This prediction leads to 24 with the relative stereochemistry shown in Scheme 2.
To support the proposed relative configuration of all of the stereocenters of 24, we performed a detailed NMR analysis ($^1$H, $^{13}$C, COSY, NOE, NOESY). The first piece of information supporting our assignment of the stereochemistry of 24 is the coupling of the $\alpha$-proton (H$_A$, 24, Figure 2). It is a triplet with a coupling constant of 12.5 Hz, indicating that it has a trans-axial relationship with two protons (H$_B$ and H$_C$). This supports our prediction of the ring fusion stereochemistry as trans. Next, an NOE on H$_D$ ($\alpha$ to the TBS ether, 24, Figure 2) did not show any through-space coupling with H$_A$. This supports our original assignment of the acyl radical precursor (23) as syn. If the relative stereochemistry of H$_B$ and H$_D$ were anti, then H$_A$ and H$_D$ would have a 1,3-diaxial relationship and should exhibit a strong NOE. Another piece of data supporting the original syn relationship of 23 is that H$_D$ appears as a broad singlet, indicating that it is coupled to multiple protons, all with small coupling constants. This splitting pattern is more characteristic of an equatorial hydrogen than of an axial hydrogen.$^8$
The relative stereochemistry of the distal methyl group was slightly more challenging to determine, although the preference for a chair-like transition state for a 6-exo-trig cyclization is widely accepted. Ideally, an NOE between H_A and H_E (24, Figure 2) would confirm the proposed stereochemistry. Unfortunately, H_A and H_E are not completely resolved on a 500 MHz $^1$H NMR (t, 2.44, $J = 12.5$ Hz and m, 2.53–2.46 respectively), preventing a conclusive NOE analysis. Consequently, in order to support the proposed stereochemistry of the methyl group, we must first suppose it to be opposite of that predicted by the chair-like transition state shown in Scheme 2. If this were the case, the six-membered ring would likely adopt a boat conformation (see epi-methyl 24, Figure 2) in order to avoid a 1,3-diaxial interaction between the TBS ether and the methyl group. Such a conformation should show a very strong NOE between H_A and H_F (the flagpole hydrogens), which is not present. This supports our original prediction of the stereochemistry of 24 as shown in Scheme 2. We are currently attempting to make a crystalline derivative of 24 to unambiguously confirm our stereochemical prediction.

In conclusion, we have demonstrated the first example of a 7-exo-trig/6-exo-trig acyl radical cascade reaction. This remarkable transformation forms two new C–C bonds and generates two stereocenters in a highly regio- and stereoselective manner. This cascade reaction should be a useful tool for the preparation of the bicyclo[5.4.0]undecane
ring system, and should have applications in total synthesis, including that of Lyconadin A as described herein.

3.3 References


4.1 Stereochemical Issues of the Radical Cascade

We have successfully demonstrated that the novel 7-exo-trig/6-exo-trig acyl radical cascade cyclization can be employed to prepare the bicyclo[5.4.0]undecane ring system in excellent yield and with a high degree of stereoselectivity. Although we have predicted the relative stereochemistry of the model acyl radical cascade product (24, Figure 1) based on chair-like transition states and we have supported that prediction with NMR data, our immediate goal is to confirm the stereochemistry of 24. We will attempt to do this by X-ray analysis of a derivative of 24. Both the alcohol (free alcohol or $p$-nitrobenzoyl ether) and the ketone (2,4-dinitrophenylhydrazine or a semicarbazone) could serve as handles for converting 24 into a crystalline derivative suitable for X-ray diffraction techniques, which would unambiguously reveal the relative stereochemistry.

![Figure 1. Model Acyl Radical Cascade Product (24)](image)

In addition to proving the stereochemistry of 24, we also need to attempt the acyl radical cascade reaction on the anti diastereomer of phenyl selenoester 23. Because the relative stereochemistry of 23 is determined during the ketone reduction step (see Scheme 8, Chapter 2) we should be able to find a reducing agent that would provide the opposite stereoselectivity to that which we observed using NaBH$_4$. For example, Zn(BH$_4$)$_2$ has been used to selectively reduce $\beta$-keto esters to products corresponding to those that would lead to anti-phenyl selenoester 23. We expect that the anti diastereomer would more strongly enforce a chair-like transition state in the radical cascade process because
the TBS ether could occupy an equatorial position. However, the stereoselectivity of the exo methyl group could be attenuated because the alkene would experience much weaker steric repulsion with a 1,3-diaxial hydrogen than with a TBS ether (see Scheme 2, Chapter 3).

4.2 Application of the Model Acyl Radical Cascade to Lyconadin A

The relevance of the model acyl radical cascade that we have accomplished to the total synthesis of Lyconadin A depends on the degree of stereoselectivity achieved and the relative stereochemistry of the product. An examination of the stereochemistry of the model radical cascade product (24, Figure 1) relative to that of the corresponding intermediate in the proposed synthesis of Lyconadin A (15, Figure 2) reveals that the α-carbon of cycloheptanone 24 (C-7, Lyconadin A numbering) is of the wrong relative stereochemistry. However, because of the high degree of stereoselectivity achieved in the model we would like to employ an analogous reaction in the total synthesis of the natural product.

Figure 2. Stereochemistry Required for the Total Synthesis of Lyconadin A

Because the stereocenter we would need to invert is alpha to a carbonyl, we envision two methods whose net effect would be to epimerize the desired stereocenter of 24. The simplest method would be kinetic protonation of the enolate derived from 24 (Scheme 1). Although the system in which the ring fusion is trans is certainly the
thermodynamic product, the axial TBS ether could cause protonation of the enolate to occur from the opposite face, which would give the *cis* ring fusion\(^3\) corresponding to the stereochemistry needed in Lyconadin A. The preference for protonation on the bottom side should be exaggerated at low temperatures and with a bulky proton source such as *tert*-butyl alcohol. Alternatively, oxidation to the enone of \(24\) using either the Saegusa protocol\(^4\) or IBX,\(^5\) followed by stereoselective reduction\(^6\) could also provide the necessary relative stereochemistry (Scheme 1). Again, the axial TBS ether should shield the top face so that the reducing agent preferentially approaches from the bottom face.

![Scheme 1. Suggested Methods for Epimerization of 24](image)

With the information we have gained about the 7-\textit{exo-trig}/6-\textit{exo-trig} acyl radical cascade cyclization from the model studies, we are now in a position to develop a more detailed stereoselective approach to Lyconadin A. Our initial proposal is described in Chapter 1 (see Scheme 2, Chapter 1), and based on our results from the model it need only be modified as shown in Scheme 2, in which the ketone is replaced with a TBS ether in a \textit{syn} relationship to the vinyl group. Again the TBS ether will occupy an axial position in the transition state, and we can expect a high degree of stereoselectivity in both cyclizations, providing the \(C_\alpha\) epimer of \(84\). Epimerization according to the results
of the reactions shown in Scheme 1 should then afford 84 with the proper relative stereochemistry. It is of note that the aminomethyl group could reinforce both the chair-like transition state of the 7-exo cyclization (it would occupy an equatorial position) and the stereoselectivity of the epimerization.

\[
\text{Scheme 2. Modified Acyl Radical Cascade Approach to Lyconadin A}
\]

4.3 Conclusion

In summary, we have proposed a synthetic route to the alkaloid Lyconadin A, in which the key step is a 7-exo-trig/6-exo-trig acyl radical cascade cyclization. We have modeled this key reaction by preparing phenyl selenoester syn-23 and exploring its behavior in the novel acyl radical cascade. This cascade proceeds in high yield and with excellent diastereoselectivity to provide the bicyclo[5.4.0]undecane ring system of 24. Unfortunately, the major diastereomer of the cyclization product contains a trans ring fusion. Consequently, an epimerization of the \(\alpha\)-carbon will be necessary in order to employ this cascade in the proposed total synthesis of Lyconadin A. Despite this, the studies we have performed on the model system have provided us with valuable information applicable to a stereoselective approach to the first total synthesis of Lyconadin A.
4.4 References


5.1 General Methods

Tetrahydrofuran, ether, \(N,N\)-dimethylformamide, methylene chloride, acetonitrile, dimethylsulfoxide, diisopropylamine, triethylamine, methanol, and benzene were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina.\(^1\) Flash chromatography was carried out using 60–230 mesh silica gel. \(^1\)H NMR spectra were obtained on either a Varian 300 MHz or a Varian 500 MHz spectrometer as indicated, with chloroform (7.27 ppm) or tetramethylsilane (0.00 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dd (doublet of doublets), dt (doublet of triplets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). \(^13\)C NMR spectra were obtained on one of two Varian spectrometers operating at 75 or 125 MHz respectively (as indicated), with chloroform (77.23 ppm) as internal reference. The intensities of \(^1\)H–\(^1\)H COSY and \(^1\)H–\(^1\)H NOESY correlations are reported as follows: w (weak), m (medium), s (strong). Infrared spectra were obtained on a Nicolet Avatar 360 FT-IR Spectrometer. Mass spectral data were obtained using FAB techniques by the Brigham Young University mass spectrometry facility.

5.2 Experimental Details

4-Methoxybenzyl 2-(2-(4-methoxybenzyloxy)ethyl)benzoate (57). To a solution of isochromanone (56, 7.88 g, 53.2 mmol) in THF (76 mL) and MeOH (30 mL)
was added aq NaOH (4 M, 106 mL, 424 mmol) dropwise, and the resulting orange
solution was stirred at rt under N₂ for 1.5 h. The reaction was quenched by slow addition
of 6 M HCl until the pH was about 2 (ca. 100 mL) and the solution extracted with EtOAc
(5 × 50 mL). The combined organic extracts were washed with H₂O (75 mL), dried
(Na₂SO₄), and concentrated in vacuo. Azeotropically drying with benzene afforded the
hydroxy acid as a white powder (8.44 g).

To a solution of the crude hydroxy acid in anhydrous THF (200 mL) and
anhydrous DMF (27 mL) was added NaH (60% in mineral oil, 5.34 g, 133.5 mmol), and
gas was evolved. 4-Methoxybenzyl chloride (21.3 mL, 24.6 g, 157 mmol) and
tetrabutylammonium iodide (16.0 g, 43.3 mmol) were added, and the mixture stirred at rt
under N₂ for 3.5 h. The reaction was quenched with 1 M HCl (100 mL) and partitioned
into EtOAc (100 mL). The organic phase was collected, the aqueous phase extracted
with EtOAc (4 × 75 mL), and the combined organics were washed with brine (2 × 100
mL), dried (Na₂SO₄), and concentrated in vacuo. Purification by flash chromatography
(SiO₂: 5.5 × 60 cm, 5–15% EtOAc in hexanes gradient elution) yielded 57 (11.41 g, 28.1
mmol, 53% over two steps) as a pale crystalline solid: ¹H NMR (CDCl₃, 300 MHz) δ
7.88 (d, J = 7.8 Hz, 1H), 7.37–7.17 (m, 7H), 6.87 (d, J = 6.6 Hz, 2H), 6.82 (d, J = 6.6 Hz,
2H), 5.23 (s, 2H), 4.37 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.64 (t, J = 6.9 Hz, 2H), 3.28 (t,
J = 6.9 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.5, 159.7, 159.1, 140.7, 131.9 (3C),
130.8, 130.2 (2C), 130.1 (2C), 129.2, 128.2, 126.3, 114.0 (2C), 113.7 (2C), 72.4, 70.8,
66.5, 55.3, 55.2, 34.9; IR (film) vₘₐₓ 3028, 2941, 2853, 1715, 1608, 1511, 1251, 1085
cm⁻¹; HRMS (FAB) m/z 429.1685 (MNa⁺, C₂₅H₂₆O₅Na requires 429.1678).
**tert-Butyldimethylsilyl chloride (12.73 g, 84.4 mmol) (or the appropriate silyl chloride) and the reaction was stirred at rt under N₂ for 23 h. The crude reaction mixture was partitioned into Et₂O and H₂O (100 mL each). The organic phase was collected and the aqueous phase was extracted with Et₂O (3 × 100 mL). The combined organics were washed with H₂O (100 mL), dried (Na₂SO₄), and concentrated in vacuo. Purification by flash chromatography (SiO₂: 5.5 × 47 cm, 5–8% Et₂O in hexanes gradient elution) afforded 58a (9.96 g, 25.8 mmol, 94%) as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 7.44–7.40 (m, 1H), 7.24–7.15 (m, 5H), 6.86 (dd, J = 6.6, 2.1 Hz, 2H), 4.75 (s, 2H), 4.44 (s, 2H), 3.78 (s, 3H), 3.64 (t, J = 7.5 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H), 0.93 (s, 9H), 0.08 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 159.4, 139.5, 139.5,
tert-Butyl(2-(2-(4-methoxybenzyloxy)ethyl)benzyloxy)diphenylsilane (58b).

The two-step procedure described above was applied to prepare 58b (319 mg, 0.625 mmol, 83%) as a colorless oil: \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.71–7.68 (m, 4H), 7.52–7.49 (m, 1H), 7.42–7.33 (m, 6H), 7.24–7.14 (m, 5H), 6.82 (dd, \(J = 6.6, 2.4\) Hz, 2H), 4.79 (s, 2H), 4.34 (s, 2H), 3.77 (s, 3H), 3.56 (t, \(J = 7.5\) Hz, 2H), 2.83 (t, \(J = 7.5\) Hz, 2H), 1.09 (s, 9H); \(^13\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 159.3, 139.1, 136.2, 135.8 (4C), 133.7 (2C), 130.7, 129.9 (2C), 129.6, 129.4 (2C), 127.9 (4C), 127.4, 127.3, 126.6, 113.9 (2C), 72.8, 70.6, 63.9, 55.4, 32.7, 27.1 (3C), 19.5; IR (film) \(\nu_{\text{max}}\) 3070, 2956, 2931, 2857, 1612, 1513, 1464, 1427, 1424, 1110, 737 cm\(^{-1}\); HRMS (FAB) \(m/z\) 409.2181 (MNa\(^+\), C\(_{23}\)H\(_{34}\)O\(_3\)SiNa requires 409.2175).

Triisopropyl(2-(2-(4-methoxybenzyloxy)ethyl)benzyloxy)silane (58c). The two-step procedure described above was applied to prepare 58c (139.5 mg, 0.325 mmol, 82%) as a colorless oil: \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.51 (d, \(J = 6.6\) Hz, 1H), 7.23–7.14 (m, 5H), 6.86 (dd, \(J = 6.6, 2.1\) Hz, 2H), 4.84 (s, 2H), 4.44 (s, 2H), 3.78 (s, 3H), 3.64 (t, \(J = 7.5\) Hz, 2H), 2.90 (t, \(J = 7.5\) Hz, 2H), 1.19–1.05 (m, 21H); \(^13\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 159.3, 139.7, 135.8, 130.7, 129.5, 129.4 (2C), 127.0, 126.8, 126.6, 113.9 (2C), 72.9, 70.6, 63.2, 55.4, 32.7, 18.3 (3C), 12.2 (6C); IR (film) \(\nu_{\text{max}}\) 2943, 2865, 1613, 1513, 1462, 1248, 1089 cm\(^{-1}\); HRMS (FAB) \(m/z\) 451.2657 (MNa\(^+\), C\(_{26}\)H\(_{40}\)O\(_3\)SiNa requires 451.2645).
2-(2-((tert-Butyldimethylsilyloxy)methyl)phenyl)ethanol (59a). Differentially protected diol 58a (9.96 g, 25.8 mmol) was dissolved in CH$_2$Cl$_2$ (200 mL) and distilled H$_2$O (10 mL), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 6.63 g, 29.2 mmol) was added. The dark green solution was stirred at rt under N$_2$ for 2.5 h, during which time the color faded to a pale pink. The reaction was quenched with sat NaHCO$_3$ (150 mL), the organic layer was collected, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 100 mL). The combined organic extracts were washed successively with sat NaHCO$_3$ and brine solution (125 mL each), dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash chromatography (SiO$_2$: 5.5 × 53 cm, 0.25–1.0% MeOH in CH$_2$Cl$_2$ gradient elution) to afford pure mono-TBS diol 59a (5.35 g, 20.1 mmol, 78%) as a colorless oil: $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.37–7.34 (m, 1H), 7.25–7.17 (m, 3H), 4.74 (s, 2H), 3.81 (dt, $J$ = 6.6, 5.7 Hz, 2H), 2.89 (t, $J$ = 6.6 Hz, 2H), 2.52 (t, $J$ = 5.7 Hz, 1H), 0.94 (s, 9H), 0.12 (s, 6H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 139.1, 137.0, 130.0, 128.3, 127.9, 126.7, 63.7, 63.4, 35.5, 26.1 (3C), 18.6, −5.1 (2C); IR (film) $\nu$$_{max}$ 3360 (br), 3065, 3026, 2941, 1464, 1383, 1253, 1064, 844, 769 cm$^{-1}$; HRMS (FAB) m/z 289.1613 (MNa$^+$, C$_{15}$H$_{26}$O$_2$SiNa requires 289.1600).

2-(2-((tert-Butyldiphenylsilyloxy)methyl)phenyl)ethanol (59b). The above procedure was applied to 58b (267 mg, 0.52 mmol, reagents and solvents scaled
appropriately) to yield the title compound (172 mg, 0.44 mmol, 84%) as a colorless oil:

\[ ^1H \text{ NMR (CDCl}_3, 300 \text{ MHz) } \delta 7.73–7.69 (m, 4H), 7.45–7.34 (m, 7H), 7.24–7.16 (m, 3H), 4.76 (s, 2H), 3.73 (t, } J = 6.6 \text{ Hz, 2H), } 2.80 (t, } J = 6.6 \text{ Hz, 2H), } 1.82 (\text{br s, 1H), 1.08 (s, 9H); } ^{13}C \text{ NMR (CDCl}_3, 75 \text{ MHz) } \delta 138.9, 136.4, 135.8 (4C), 133.5 (2C), 130.0 (2C), 129.9, 128.2, 128.0 (4C), 127.7, 126.8, 64.1, 63.2, 35.5, 27.0 (3C), 19.4; \text{ IR (film) } \nu_{\text{max}} 3372 (\text{br}), 3070, 2932, 2857, 1470, 1427, 1112, 1076, 823, 741, 703 \text{ cm}^{-1}; \text{ HRMS (FAB) } m/z 413.1906 (MNa}^+{, C_{25}H_{30}O_2SiNa \text{ requires 413.1913}).

2-(2-((Triisopropylsilyloxy)methyl)phenyl)ethanol (59c). The above procedure was applied to 58c (140 mg, 0.33 mmol, reagents and solvents scaled appropriately) to yield the title compound (63 mg, 0.20 mmol, 62%) as a colorless oil: \[ ^1H \text{ NMR (CDCl}_3, 300 \text{ MHz) } \delta 7.46–7.43 (m, 1H), 7.26–7.18 (m, 3H), 4.83 (s, 2H), 3.85 (t, } J = 6.3 \text{ Hz, 2H), 2.90 (t, } J = 6.3 \text{ Hz, 2H), 2.17 (br s, 1H), 1.25–1.07 (m, 21H); \text{ IR (film) } \nu_{\text{max}} 3350, 2943, 2866, 1463, 1383, 1122, 1065, 882, 682 \text{ cm}^{-1}; \text{ HRMS (FAB) } m/z 309.2260 (MH}^+{, C_{18}H_{33}O_2Si \text{ requires 309.2249}).

(2-(2-Bromoethyl)benzyloxy)(tert-butyl)dimethylsilane (55a). LiBr (17.6 g, 203 mmol) was thoroughly flame dried under reduced pressure, cooled, and suspended in anhydrous THF (190 mL). Alcohol 59a (5.35 g, 20.1 mmol) in anhydrous THF (10 mL) was added, followed by Et\text{}_3N (7.0 mL, 5.08 g, 50.2 mmol) and methanesulfonyl chloride (3.4 mL, 5.03 g, 43.9 mmol). The solution was stirred at rt under N\text{\textsubscript{2}} for 6 days,
quenched with H₂O (150 mL), and extracted with Et₂O (4 × 75 mL). The combined extracts were washed with H₂O (100 mL), dried (Na₂SO₄), and concentrated in vacuo to give 55a (6.17 g, 18.7 mmol, 93%) as a yellow oil. The crude material typically needed no purification, although an analytical sample could be purified by flash chromatography (SiO₂: 1.4 × 22 cm; 5% Et₂O in hexanes). ¹H NMR (CDCl₃, 300 MHz) δ 7.38–7.35 (m, 1H), 7.25–7.16 (m, 3H), 4.73 (s, 2H), 3.56 (t, J = 8.1 Hz, 2H), 3.19 (t, J = 8.1 Hz, 2H), 0.94 (s, 9H), 0.11 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 139.1, 137.1, 129.8, 128.5, 127.9, 127.3, 63.8, 36.4, 32.5, 26.2 (3C), 18.6, −5.0 (2C); IR (film) νₘₐₓ 3023, 2942, 2869, 1463, 1384, 1254, 1071, 843, 770 cm⁻¹; HRMS (FAB) m/z 351.0763 (MNa⁺, C₁₅H₂₅OBrSiNa requires 351.0756).

(2-(2-Bromoethyl)benzyloxy)(tert-butyl)diphenylsilane (55b). The above procedure was applied to 59b (82 mg, 0.21 mmol, reagents and solvents scaled appropriately). The crude product was purified by flash chromatography (SiO₂: 1.5 × 13.5 cm; 1:10 Et₂O in hexanes) to yield the pure title compound (73 mg, 0.16 mmol, 77%) as a white, amorphous solid: ¹H NMR (CDCl₃, 300 MHz) δ 7.72–7.68 (m, 4H), 7.44–7.36 (m, 7H), 7.27–7.23 (m, 2H), 7.20–7.16 (m, 1H), 4.73 (s, 2H), 3.50 (t, J = 8.1 Hz, 2H), 3.13 (t, J = 8.1 Hz, 2H), 1.08 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 138.8, 136.9, 135.9 (4C), 133.5 (2C), 130.0 (2C), 129.7, 128.5, 128.0 (4C), 127.8, 127.3, 64.2, 36.2, 32.4, 27.1 (3C), 19.5; IR (film) νₘₐₓ 3070, 2958, 2931, 2857, 1471, 1428, 1110, 1068, 738, 704 cm⁻¹; HRMS (FAB) m/z 475.1068 (MNa⁺, C₂₅H₂₉OBrSiNa requires 475.1069).

(2-(2-Bromoethyl)benzyloxy)triisopropylsilane (55c). The above procedure was applied to 59c (59 mg, 0.19 mmol, reagents and solvents scaled appropriately) to
yield the pure title compound (66 mg, 0.18 mmol, 93%) without need for purification, as a yellow oil: ¹H NMR (CDCl₃, 300 MHz) δ 7.46–7.43 (m, 1H), 7.27–7.17 (m, 3H), 4.82 (s, 2H), 3.58 (t, J = 7.8 Hz, 2H), 3.20 (t, J = 7.8 Hz, 2H), 1.25–1.02 (m, 21H); ¹³C NMR (CDCl₃, 75 MHz) δ 139.4, 136.8, 129.6, 128.1, 127.7, 127.3, 63.8, 36.3, 32.5, 18.3 (6C), 12.3 (3C); IR (film) ν max 2943, 2866, 1462, 1108, 1065, 883, 806, 736, 683, 648 cm⁻¹; HRMS (FAB) m/z not available (MNa⁺, C₁₈H₃₁OBrSiNa requires 393.1225).

Ethyl 2-(2-((tert-butyldimethylsilyloxy)methyl)phenethyl)-5-(4-methoxybenzyloxy)-3-oxopentanoate (65). To a suspension of NaH (60% dispersion in mineral oil, 12 mg, 0.31 mmol) in anhydrous THF (0.2 mL) was added β-keto ester 64 (85 mg, 0.30 mmol) dropwise in anhydrous THF (0.2 mL), with violent evolution of gas. Bromide 55a (53 mg, 0.16 mmol) in anhydrous THF (0.2 mL) was then added, and most of the solvent was removed in vacuo and replaced with a solution of NaI (12 mg, 0.08 mmol) in anhydrous acetonitrile (0.50 mL). The reaction mixture was then heated to 60 °C and stirred under Ar for 29 h, cooled, diluted with Et₂O (1.0 mL), and quenched with 1 M HCl (0.5 mL). The organic phase was collected, and the aqueous phase was extracted with Et₂O (1.0 mL). The combined organic phases were washed with H₂O (1.0 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂: 2.5 × 25 cm; 10–11% EtOAc in hexanes gradient elution) to give a 3:1 mixture of the iodo and styrene derivatives of bromide 55a (30 mg, 0.065 mmol iodide, 0.22 mmol styrene) and the title compound (40 mg, 0.076 mmol, 47%, 78% based
on recovered iodide) in equilibrium with its enol tautomer, as a yellow oil: $^1\text{H}\text{NMR (CDCl}_3, 300 \text{ MHz}) \delta 7.43–7.40 (m, 1H), 7.24–7.09 (m, 5H), 6.85 (d, $J = 8.7 \text{ Hz}, 2H), 4.73 (s, 2H), 4.41 (s, 2H), 4.16 (q, $J = 6.9 \text{ Hz}, 2H), 3.78 (s, 3H), 3.70 (t, $J = 6.3 \text{ Hz}, 2H), 3.53 (t, $J = 7.2 \text{ Hz}, 1H), 2.82–2.76 (m, 2H), 2.62–2.56 (m, 2H), 2.13 (q, $J = 7.8 \text{ Hz}, 2H), 1.25 (t, $J = 6.9 \text{ Hz}, 3H), 0.93 (s, 9H), 0.10 (s, 6H); ^{13}\text{C NMR (CDCl}_3, 75 \text{ MHz}) \delta 203.5, 169.6, 159.4, 139.1, 138.2, 130.3, 129.5 (2C), 129.2, 127.5, 127.4, 126.5, 113.9 (2C), 73.1, 64.9, 63.0, 61.6, 59.2, 55.4, 42.2, 29.9, 28.9, 26.1 (3C), 18.5, 14.3, –5.1 (2C); IR (film) not collected; HRMS (FAB) $m/z$ 551.2800 (MNa$^+$, C$_{30}$H$_{44}$O$_6$SiNa requires 551.2805).

Diethyl 2,2'-((1,3-dioxolane-2,2-diyl)diacate (67). In a 3-neck round bottom flask, $p$-toluenesulfonic acid monohydrate (1.08 g, 5.7 mmol) was dissolved in benzene (115 mL), and ethylene glycol (2.3 mL, 41.2 mmol) was added. The round bottom flask was equipped with a Dean–Stark apparatus, and the mixture was refluxed for 1 h. Diethyl acetone-1,3-dicarboxylate (DEADC, 66, 5.0 mL, 5.6 g, 27.5 mmol) was added and the reaction refluxed for 6 h, cooled to rt, quenched with sat NaHCO$_3$ (50 mL) and stirred for 15 min. The organic phase was collected, and the aqueous phase extracted with EtOAc (4 × 50 mL). The combined organics were washed with sat NaHCO$_3$ and brine solution (50 mL each), dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash chromatography (SiO$_2$: 5.5 × 63 cm; 10–25% EtOAc in hexanes gradient elution) to give 1,3-dioxolane 67 (3.65 g, 14.8 mmol, 54%) as a yellow oil: $^1\text{H NMR (CDCl}_3, 300 \text{ MHz}) \delta 4.16 (q, $J = 6.6 \text{ Hz}, 4H), 4.03 (s, 4H), 2.94 (s, 4H), 1.27 (t,
$J = 6.6 \text{ Hz}, 6H$; $^{13}\text{C NMR (CDCl}_3, 75 \text{ MHz}) \delta 169.4 (2C), 107.0, 65.3 (2C), 60.7 (2C), 42.4 (2C), 14.3 (2C)$; IR (film) $\nu_{\text{max}} 2978, 2904, 1736, 1325–1112, 1036, 736 \text{ cm}^{-1}$; HRMS (FAB) $m/z$ 269.0984 ($\text{MNa}^+$, $\text{C}_{11}\text{H}_{18}\text{O}_6\text{Na}$ requires 269.1001).

**2,2-Bis(2-(4-methoxybenzyl)oxy)ethyl)-1,3-dioxolane (68).** To a solution of 67 (346 mg, 1.40 mmol) in anhydrous THF (14 mL) was added LAH (1.0 M in THF, 2.1 mL, 2.1 mmol) dropwise with evolution of gas. The slurry was stirred at rt under N$_2$ overnight then quenched by successive dropwise addition of H$_2$O (80 μL) with violent evolution of gas, 15% aq NaOH (80 μL), and H$_2$O (240 μL). The slurry was dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo.

To a solution of the crude diol (214 mg) in anhydrous DMF (5.6 mL) was added NaH (60% dispersion in mineral oil, 166 mg, 4.15 mmol) with evolution of gas. The solution was stirred under Ar at rt for 50 min, after which $p$-methoxybenzyl chloride (575 μL, 664 mg, 4.24 mmol) was added dropwise, followed by tetrabutylammonium iodide (208 mg, 0.56 mmol). The resulting mixture was stirred under Ar at rt for 24 h, then at 70 °C for 17 h. TLC analysis indicated incomplete conversion, so more NaH (60% dispersion in mineral oil, 175 mg, 4.38 mmol) and $p$-methoxybenzyl chloride (400 μL, 462 mg, 2.95 mmol) were added, and the reaction stirred under Ar at 70 °C for an additional 23 h. The reaction was cooled to 0 °C, quenched with 1 M HCl (10 mL), and extracted with EtOAc (4 × 5 mL). The combined organic extracts were washed with brine (15 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash chromatography (SiO$_2$: 3.2 × 41 cm; 10–25% acetone in hexanes gradient elution)
to give the mono-protected diol (145 mg, 0.51 mmol, 37% over 2 steps) and the title
compound (133 mg, 0.33 mmol, 24% over 2 steps, 37% based on recovered mono-
protected diol) as a yellow oil: \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.24 (d, \(J = 8.7\) Hz, 4H),
6.86 (d, \(J = 8.7\) Hz, 4H), 4.40 (s, 4H), 3.90 (s, 4H), 3.79 (s, 6H), 3.55 (t, \(J = 7.2\) Hz, 4H),
1.98 (t, \(J = 7.2\) Hz, 4H); \(^1\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 159.3 (2C), 130.8 (2C), 129.5
(4C), 114.0 (4C), 109.7, 72.9 (2C), 66.1 (2C), 65.0 (2C), 55.4 (2C), 37.6 (2C); IR (film)
\(\nu_{\text{max}}\) 2945, 2878, 1726, 1610, 1511, 1460, 1367, 1247, 1169, 1090, 914 cm\(^{-1}\); HRMS
(FAB) \(m/z\) not collected (MNa\(^+\), \(C_{23}H_{30}O_6\)Na requires 425.1940).

\[ \text{PMBO} \quad \text{O} \quad \text{OPMB} \]

\textbf{1,5-Bis(4-methoxybenzyl)oxy)pentan-3-one (69).} To a solution of 68 (133 mg,
0.33 mmol) in acetone (6 mL) and H\(_2\)O (0.30 mL) was added pyridinium
\(p\)-toluenesulfonate (36 mg, 0.14 mmol). The mixture was refluxed for 19 h, cooled,
poured into EtOAc (7 mL), washed with sat NaHCO\(_3\) (2 \(\times\) 5 mL) and brine (5 mL), dried
(Na\(_2\)SO\(_4\)), and concentrated in vacuo. The residue was purified by flash chromatography
(SiO\(_2\): 2.5 \(\times\) 30 cm; 10–12% acetone in hexanes gradient elution) to give 69 (78 mg, 0.21
mmol, 63%), contaminated with a trace of PMB-OH. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.23
(d, \(J = 8.7\) Hz, 4H), 6.86 (d, \(J = 8.7\) Hz, 4H), 4.43 (s, 4H), 3.80 (s, 6H), 3.71 (t, \(J = 6.3\)
Hz, 4H), 2.72 (t, \(J = 6.3\) Hz, 4H); \(^1\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 207.8, 159.5 (2C), 130.5
(2C), 129.6 (4C), 114.0 (4C), 73.1 (2C), 65.1 (2C), 55.5 (2C), 43.7 (2C); IR (film) \(\nu_{\text{max}}\)
not collected cm\(^{-1}\); HRMS (FAB) \(m/z\) not collected (MNa\(^+\), \(C_{21}H_{26}O_5\)Na requires
381.1678).
Diethyl 2-((tert-butyldimethylsilyloxy)methyl)phenethyl)-3-oxopentanediolate (72). To a suspension of NaH (60% dispersion in mineral oil, 257 mg, 6.42 mmol) in anhydrous THF (10 mL) at 0 °C under Ar was added diethyl acetone-1,3-dicarboxylate (DEADC, \(66\), 1.16 mL, 1.29 g, 6.39 mmol) dropwise, with rapid evolution of gas. The mixture was stirred at 0 °C for 10 min, bromide \(55a\) (450 μL, 513 mg, 1.56 mmol) was added, and most of the THF was removed in vacuo. The sticky orange residue was dissolved in anhydrous acetonitrile (5.0 mL), NaI (118 mg, 0.79 mmol) was added, and the mixture heated at 60 °C under Ar for 6.75 days, after which most of the solvent had evaporated. The residue was cooled to rt, diluted with EtOAc (7 mL) and quenched with 1 M HCl (6 mL). The organic phase was collected and the aqueous phase extracted with EtOAc (3 × 6 mL). The combined organic phases were washed with brine (10 mL), dried (\(\text{Na}_2\text{SO}_4\)), and concentrated in vacuo. The residue was purified by flash chromatography (SiO\(_2\): 3.2 × 37 cm; 10% EtOAc in hexanes) to give the title compound (590 mg, 1.31 mmol, 84%) in equilibrium with multiple enol tautomers, as a yellow oil: \(^1\text{H NMR (CDCl}_3, 300 \text{ MHz}) \delta 7.44–7.41 (m, 1H), 7.24–7.18 (m, 2H), 7.15–7.12 (m, 1H), 4.74 (s, 2H), 4.26–4.15 (m, 4H), 3.68 (t, \(J = 7.2 \text{ Hz}, 1H\)), 3.60 (d, \(J = 15.9 \text{ Hz}, 1H\)), 3.55 (d, \(J = 15.9 \text{ Hz}, 1H\)), 2.65–2.60 (m, 2H), 2.20–2.12 (m, 2H), 1.31–1.24 (m, 6H), 0.94 (s, 9H), 0.10 (s, 6H); \(^{13}\text{C NMR (CDCl}_3, 75 \text{ MHz}) \delta 197.5, 169.1, 166.8, 139.1, 138.0, 129.2, 127.6, 127.4, 126.6, 63.0, 61.9, 61.7, 58.7, 48.3, 29.9, 28.9, 26.1 (3C), 18.6, 14.2 (2C), −5.1 (2C); IR (film) \(\nu_{\text{max}}\) 2934, 2858, 1741, 1650, 1464, 1370, 1
1317, 1251, 1077, 842, 776 cm⁻¹; HRMS (FAB) m/z 473.2342 (MNa⁺, C₂₄H₃₈O₆SiNa requires 473.2335).

**syn-3-(**tert-**Butyldimethylsilyloxy)-2-(2-((**tert-**Butyldimethylsilyloxy)methyl)**phenethyl)-**N¹,N⁵-dimethoxy-**N¹,N⁵-dimethylpentanediamide (73).** To a solution of ketoester 72 (163 mg, 0.36 mmol) in MeOH (3.5 mL) at 0 °C was added NaBH₄ (30 mg, 0.78 mmol) with some gas evolution. The solution was stirred under N₂ at 0 °C for 15 min, quenched with sat NH₄Cl (3 mL), and extracted with CH₂Cl₂ (4 × 3 mL). The combined extracts were dried (Na₂SO₄), and concentrated in vacuo.

To a solution of the crude alcohol (176 mg) in anhydrous CH₂Cl₂ (1.8 mL) at 0 °C under Ar was added 2,6-lutidine (130 μL, 120 mg, 1.12 mmol) and 5 min later tert-butyldimethylsilyl trifluoromethanesulfonate (166 μL, 191 mg, 0.72 mmol). The reaction was stirred under Ar and allowed to warm to room temperature over 43 h, then poured into sat NaHCO₃ (2 mL). The organic phase was collected and the aqueous phase extracted with CH₂Cl₂ (3 × 2 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo, then purified by flash chromatography (SiO₂: 2.1 × 19 cm, 5% EtOAc in hexanes) to afford the diester analogue of 73 (122 mg, 0.22 mmol, 60%, ca. 2:1 mixture of diastereomers) as a yellow oil: ¹H NMR (CDCl₃, 300 MHz) δ 7.46–7.41 (m, 1H), 7.23–7.16 (m, 2H), 7.13–7.10 (m, 1H), 4.75 and 4.74 (2s, 2H), 4.45–4.36 (m, 1H), 4.21–4.06 (m, 4H), 2.70–2.60 (m, 2H), 2.57–2.41 (m, 3H), 1.98–1.72 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.94 (s, 9H), 0.84 (s, 9H), 0.10 (s, 6H), 0.06 and

58
0.04 (2s, 3H), 0.03 and 0.01 (2s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 173.6 and 173.5, 171.8 and 171.6, 139.0 and 138.9, 138.7 and 138.6, 129.1 and 129.0, 127.3 and 127.3, 127.2 and 127.1, 126.3, 70.8 and 70.3, 63.0 and 62.8, 60.6 and 60.6, 52.2 and 51.7, 40.0 and 39.7, 30.6 and 30.5, 29.4, 27.9, 26.1 (3C), 25.8 (3C), 18.5, 18.1 and 18.1, 14.5, 14.3, –4.6 and –4.7, –4.8, –5.1 (2C); IR (film) $\nu_{\text{max}}$ 2934, 2859, 1735, 1465, 1378, 1254, 1182, 1083, 838, 777 cm$^{-1}$; HRMS (FAB) $m/z$ 589.3365 (MNa$^+$, $C_{30}H_{54}O_6Si_2$Na requires 589.3357).

To a stirred suspension of MeNH(OMe)•HCl (106 mg, 1.09 mmol) in anhydrous THF (2.0 mL) at –10 ºC (ice/acetone bath) under Ar was added $i$-PrMgCl (2.0 M in THF, 1.1 mL, 2.2 mmol) dropwise with bubbling. After stirring for several min at –10 ºC, the diester described above (244 mg, 0.43 mmol) in anhydrous THF (0.8 mL + 0.4 mL rinse) was added, and the mixture was stirred under Ar and allowed to warm to rt for 26 hours, then quenched with sat NH$_4$Cl (5 mL) and extracted with CH$_2$Cl$_2$ (4 × 5 mL). The combined extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO$_2$: 2.4 × 23 cm, 2% MeOH in CH$_2$Cl$_2$) to afford bis-Weinreb amide 73 (184 mg, 0.308 mmol, 72%, mixture of diastereomers possibly including $E$/Z Weinreb amides) as an orange residue: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.47–7.42 (m, 1H), 7.22–7.16 (m, 3H), 4.76 (s, 1H), 4.75 (s, 1H), 4.62–4.53 (m, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 3.21 (s, 3H), 3.14–3.05 (m, 1H), 3.13 (s, 3H), 2.74–2.52 (m, 2H), 2.52–2.37 (m, 2H), 2.08–1.88 (m, 2H), 0.94 (s, 9H), 0.85 (s, 9H), 0.10 (s, 6H), 0.06 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 173.7, 172.6, 139.1, 139.0, 129.2, 127.1, 127.0, 126.2, 68.8, 62.7, 61.5, 61.4, 48.3 (2C), 35.6 (2C), 30.6 (2C), 26.1 (3C), 25.9 (3C), 18.6, 18.1, –4.8 (2C), –5.1 (2C); IR (film) $\nu_{\text{max}}$ 2935, 2893, 2858, 1663, 1464,
1386, 1254, 1077, 839 cm\(^{-1}\); HRMS (FAB) \(m/z\) 619.3579 (MNa\(^+\), \(C_{30}H_{56}O_6N_2Si_2Na\) requires 619.3575).

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**syn-3-(tert-Butyldimethylsilyloxy)-2-(2-(tert-butyldimethylsilyloxy)methyl)phenethyl)-N-methoxy-N-methylhex-5-enamide (74).** To a solution of bis-Weinreb amide syn-73 (184 mg, 0.31 mmol) in anhydrous THF (1.8 mL) under Ar at –78 °C was added DIBAL (1.0 M in THF, 1.23 mL, 1.23 mmol) dropwise, and the solution was stirred at –78 °C under Ar for 2.0 h then quenched by addition of sat aq potassium sodium tartrate (5.0 mL). The quenched mixture was allowed to warm to rt and stirred vigorously at rt for 1.0 h, then extracted with CH\(_2\)Cl\(_2\) (4 \(\times\) 4 mL). The combined extracts were washed with brine (5 mL), dried (Na\(_2\)SO\(_4\)), filtered, and concentrated in vacuo to give the crude monoaldehyde (192 mg).

To a suspension of methyltriphenylphosphonium bromide (359 mg, 1.01 mmol) in anhydrous THF (2.0 mL) under Ar was added \(n\)-BuLi (1.6 M in hexanes, 0.54 mL, 0.86 mmol) dropwise, and the yellow solution was stirred at rt for 10 min then cooled to –78 °C. The crude monoaldehyde (192 mg) in anhydrous THF (0.4 mL + 2 \(\times\) 0.3 mL rinses) was then added dropwise, and the solution was stirred under Ar and allowed to warm from –78 °C to rt over 18.5 h, then quenched with sat aq NH\(_4\)Cl (3 mL). The mixture was then extracted with EtOAc (4 \(\times\) 3 mL), and the combined extracts were washed with brine (7 mL), dried (Na\(_2\)SO\(_4\)), and concentrated in vacuo. The residue was purified by flash chromatography (SiO\(_2\): 2.4 \(\times\) 22 cm, 0.5% MeOH in CH\(_2\)Cl\(_2\)) to afford
Weinreb amide *syn*-74 (95 mg, 0.18 mmol, 57% over two steps) as a yellow oil: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.43–7.40 (m, 1H), 7.22–7.11 (m, 3H), 5.97–5.82 (m, 1H), 5.10–5.01 (m, 2H), 4.74 (d, $J$ = 13.2 Hz, 1H), 4.69 (d, $J$ = 13.2 Hz, 1H), 4.01 (quin, $J$ = 4.2 Hz, 1H), 3.69 (s, 3H), 3.23–3.12 (m, 1H), 3.20 (s, 3H), 2.49 (t, $J$ = 8.1 Hz, 2H), 2.39–2.30 (m, 1H), 2.28–2.16 (m, 1H), 1.91–1.78 (m, 1H), 1.75–1.63 (m, 1H), 0.94 (s, 9H), 0.86 (s, 9H), 0.09 (s, 6H), 0.05 (s, 3H), 0.00 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 175.2, 139.1, 138.9, 134.4, 129.0, 127.2, 127.2, 126.2, 117.5, 72.6, 62.8, 61.4, 46.5, 38.4, 30.0, 29.0, 26.2 (3C), 26.0 (3C), 18.6, 18.2, −4.6, −4.6, −5.1 (2C); IR (film) $\nu_{\text{max}}$ 2933, 2858, 1661, 1465, 1254, 1075, 839, 776 cm$^{-1}$; HRMS (FAB) $m/z$ 558.3409 (MNa$^+$, C$_{29}$H$_{53}$O$_4$NSi$_2$Na requires 558.3410).

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**syn-4-(tert-Butyldimethylsilyloxy)-3-(2-(tert-butyldimethylsilyloxy)methyl)phenethyl)-1,6-heptadiene (75).** To a solution of Weinreb amide *syn*-74 (131 mg, 0.24 mmol) in anhydrous THF (1.3 mL) under Ar at −78 ºC was added DIBAL (1.0 M in THF, 1.22 mL, 1.22 mmol) dropwise, and the solution was stirred at −78 ºC under Ar for 6 h then poured into a stirred solution of sat aq potassium sodium tartrate (5.0 mL). The quenched mixture was stirred vigorously at rt for 2.5 h, then diluted with H$_2$O (2.0 mL) and extracted with CH$_2$Cl$_2$ (4 × 4 mL). The combined extracts were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo to give the crude aldehyde, which was combined with another portion of the identical aldehyde (43 mg, 0.09 mmol).
To a suspension of methyltriphenylphosphonium bromide (523 mg, 1.55 mmol) in anhydrous THF (1.4 mL) under Ar was added n-BuLi (1.4 M in hexanes, 1.0 mL, 1.4 mmol) dropwise. The red solution was stirred at rt for 10 min then cooled to −78 ºC, then added dropwise via syringe to a solution of the mixture of aldehydes (149 mg) in anhydrous THF (1.0 mL) also at −78 ºC. The solution was stirred under Ar and allowed to warm from −78 ºC to rt over 18 h, then poured into sat aq NH₄Cl (5 mL). The mixture was then extracted with EtOAc (4 × 3 mL), and the combined extracts were dried (Na₂SO₄), and concentrated in vacuo. The crude product was purified by flash chromatography (SiO₂: 2.4 × 20 cm, 2% Et₂O in hexanes) to afford diene syn-75 (90 mg, 0.19 mmol, 58% over two steps) as a colorless oil: ¹H NMR (CDCl₃, 300 MHz) δ 7.45–7.40 (m, 1H), 7.23–7.10 (m, 3H), 5.81–5.67 (m, 2H), 5.17 (dd, J = 10.2, 1.8 Hz, 1H), 5.11–4.98 (m, 3H), 3.65 (dt, J = 6.3, 3.0 Hz, 1H), 2.69–2.59 (m, 1H), 2.47–2.37 (m, 1H), 2.29–2.10 (m, 3H), 1.81–1.69 (m, 1H), 1.66–1.51 (m, 1H), 0.94 (s, 9H), 0.88 (s, 9H), 0.10 (s, 6H), 0.03 (s, 3H), 0.01 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 139.8, 139.0, 138.9, 135.8, 128.9, 127.2, 127.1, 126.0, 117.4, 117.0, 75.5, 63.0, 49.7, 39.5, 31.7, 30.3, 26.2 (3C), 26.1 (3C), 18.7, 18.3, −3.9, −4.2, −5.0 (2C); IR (film) ν max 3074, 2955, 2929, 2857, 1472, 1255, 1077, 912, 837, 775 cm⁻¹; HRMS (FAB) m/z 497.3249 (MNa⁺, C₂₈H₅₀O₂Si₂Na requires 497.3247).

(2-(syn-4-(tert-Butyldimethylsilyloxy)-3-vinylhept-6-enyl)phenyl)methanol (76). To a solution of diene 75 (87 mg, 0.18 mmol) in CH₂Cl₂ (1.9 mL) at 0 ºC under Ar
was added a solution of (1S)-(+-)(10)-camphorsulfonic acid (9.3 mg, 0.04 mmol) in MeOH (1.9 mL). The mixture was stirred at 0 °C under Ar for 1 h and 40 min, then poured into sat aq NaHCO₃ (3 mL) and diluted with CH₂Cl₂ and H₂O (1 mL each). The organic phase was collected and the aqueous phase extracted with CH₂Cl₂ (3 × 3 mL). The combined organics were dried (Na₂SO₄) and concentrated in vacuo, then purified by flash chromatography (SiO₂: 1.5 × 16.5 cm, 7% EtOAc in hexanes) to afford benzyl alcohol 76 (57 mg, 0.16 mmol, 87%) as a yellow oil: ¹H NMR (CDCl₃, 300 MHz) δ 7.39–7.34 (m, 1H), 7.26–7.15 (m, 3H), 5.81–5.67 (m, 2H), 5.17 (dd, J = 10.2, 1.8 Hz, 1H), 5.11–4.98 (m, 3H), 4.68 (s, 2H), 3.65 (dt, J = 6.3, 3.3 Hz, 1H), 2.77–2.66 (m, 1H), 2.55–2.44 (m, 1H), 2.29–2.10 (m, 3H), 1.83–1.71 (m, 1H), 1.67–1.54 (m, 2H), 0.87 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 140.9, 139.0, 138.5, 135.8, 129.5, 128.3, 128.1, 126.3, 117.4, 117.0, 75.4, 63.2, 49.6, 39.4, 32.1, 30.5, 26.1 (3C), 18.3, –4.0, –4.3; IR (film) νmax 3332 (br), 3075, 2955, 2928, 2857, 1466, 1254, 1089, 914, 836, 775 cm⁻¹; HRMS (FAB) m/z 383.2373 (MNa⁺, C₂₂H₃₆O₂SiNa requires 383.2382).

**Se-Phenyl 2-(syn-4-(tert-butyldimethylsilyloxy)-3-vinylhept-6-enyl)benzoselenoate (23).** To a solution of oxalyl chloride (51 μL, 74 mg, 0.58 mmol) in anhydrous CH₂Cl₂ (1.0 mL) under Ar at –78 °C was added DMSO (80 μL, 88 mg, 1.13 mmol) in anhydrous CH₂Cl₂ (0.6 mL) dropwise. The solution was stirred under Ar at –78 °C for 15 min, then benzyl alcohol 76 (66 mg, 0.18 mmol) was added in anhydrous
CH₂Cl₂ (0.5 mL + 2 × 0.5 mL rinses) and the resulting solution stirred under Ar at –78 ºC for 80 min. Et₃N (260 µL, 189 mg, 1.87 mmol) in anhydrous CH₂Cl₂ (0.6 mL) was then added, and stirring continued as the mixture warmed from –78 ºC to +10 ºC over 2.5 h. The reaction was then quenched with sat aq NaHCO₃ (3 mL). The organic phase was collected and the aqueous phase extracted with CH₂Cl₂ (3 × 3 mL). The combined organics were dried (Na₂SO₄) and concentrated in vacuo to give the aldehyde (67 mg).

To a solution of the crude aldehyde in t-BuOH (2.0 mL) and H₂O (0.5 mL) was added successively 2-methyl-2-butene (0.24 mL, 156 mg, 2.23 mmol), NaH₂PO₄ (28 mg, 0.24 mmol), and NaOClO (102 mg, 1.13 mmol). The orange solution was stirred at rt under Ar for 13 h and 45 min, after which it had faded to a clear solution. It was then quenched with sat aq NH₄Cl (3 mL) and extracted with CH₂Cl₂ (4 × 3 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give the benzoic acid (71 mg).

To a solution of the crude acid in anhydrous CH₂Cl₂ (1.8 mL) under Ar was added PhSeSePh (0.28 mL of a 1.0 M solution in CH₂Cl₂, 0.28 mmol) and Bu₃P (0.11 mL, 86 mg, 0.43 mmol) dropwise. The orange solution was stirred under Ar at rt for 5 h and 40 min, after which TLC analysis indicated incomplete conversion. More PhSeSePh (0.15 mL of a 1.0 M solution in CH₂Cl₂, 0.15 mmol) and Bu₃P (75 µL, 62 mg, 0.30 mmol) were added, and the solution stirred at rt under Ar for an additional 2.5 h, then quenched with sat aq NH₄Cl (3 mL). The organic phase was collected and the aqueous phase extracted with CH₂Cl₂ (3 × 3 mL). The combined organics were dried (Na₂SO₄) and concentrated in vacuo, then purified by flash chromatography (SiO₂: 2.4 × 28 cm, 1% Et₂O in hexanes) to afford phenyl selenoester syn-23 (81 mg, 0.16 mmol, 87% over three
steps) as a yellow oil: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.82 (d, \(J = 8\) Hz, 1H), 7.61–7.58 (m, 2H), 7.45–7.40 (m, 4H), 7.31 (t, \(J = 8.0\) Hz, 1H), 7.27–7.23 (m, 1H), 5.75–5.66 (m, 2H), 5.13 (dd, \(J = 10.5, 2.0\) Hz, 1H), 5.05–4.97 (m, 3H), 3.62 (dt, \(J = 6.5, 3.5\) Hz, 1H), 2.88–2.82 (m, 1H), 2.67–2.60 (m, 1H), 2.24–2.08 (m, 3H), 1.81–1.72 (m, 1H), 1.66–1.57 (m, 1H), 0.85 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 195.6, 141.0, 139.0, 136.2 (2C), 135.7, 133.2, 132.1, 131.1, 129.6 (2C), 129.4, 129.1, 128.7, 126.2, 117.4, 117.0, 75.3, 49.3, 39.6, 32.6, 31.6, 26.1 (3C), 18.3, −4.0, −4.2; IR (film) \(\nu_{\text{max}}\) 3073, 2954, 2928, 2856, 1703, 1477, 1254, 1090, 912, 836, 736 cm\(^{-1}\); HRMS (FAB) \(m/z\) 537.1702 (MNa\(^+\), \(C_{28}H_{38}O_2SeSiNa\) requires 537.1704).

Acyl radical cascade cyclization product ((±)-24). Phenyl selenoester syn-23 (28 mg, 0.055 mmol) was dried azeotropically with anhydrous benzene (2 × 2.5 mL), then dissolved in anhydrous benzene (12 mL) in a 3-neck round-bottom flask. (TMS)\(_3\)SiH (34 \(\mu\)L, 27 mg, 0.11 mmol) and Et\(_3\)B (0.10 mL of a 1.0 M solution in hexanes, 0.10 mmol) were added, and a constant supply of dry air was provided by passing compressed air through a short tube of drierite and over the solution (venting with a needle allowed a continuous flow). An additional portion of Et\(_3\)B (1.0 mL of a 1.0 M solution in hexanes, 1.0 mmol) was added by syringe pump (0.13 mL/h, 8 h) while the solution was stirred and exposed to dry air as explained above. Following the 8 h addition period TLC analysis indicated incomplete conversion. More (TMS)\(_3\)SiH (34 \(\mu\)L, 27 mg, 0.11 mmol) was added as well as another portion of Et\(_3\)B (1.0 mL of a 1.0 M
solution in hexanes, 1.0 mmol) by syringe pump (0.08 mL/h, 12.5 h) while the reaction mixture was still exposed to dry air. The solution was stirred for an additional 3 h then concentrated in vacuo. The residue was purified by flash chromatography (SiO$_2$: 1.5 × 17 cm, 3% Et$_2$O in hexanes) to afford (±)-24 (18 mg, 0.051 mmol, 93%) as a yellow oil: $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.33 (dt, $J = 7.5, 1.5$ Hz, 1H), 7.24 (dt, $J = 7.5, 1.0$ Hz, 1H), 7.18 (d, $J = 7.5$ Hz, 1H), 7.14 (dd, $J = 7.5, 1.5$ Hz, 1H), 4.02 (br s, 1H), 2.79–2.69 (m, 3H), 2.53–2.46 (m, 1H), 2.44 (t, $J = 12.5$ Hz, 1H), 2.07–1.99 (m, 1H), 1.78–1.73 (m, 1H), 1.71–1.61 (m, 3H), 1.32–1.26 (m, 1H), 0.90 (d, $J = 7.5$ Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 212.4, 142.9, 138.2, 129.9, 129.6, 126.2, 123.5, 76.0, 51.3, 48.8, 43.2, 40.9, 34.6, 32.7, 31.4, 26.0 (3C), 18.3, 15.9, –4.4, –4.8; 2D $^1$H–$^1$H COSY NMR (CDCl$_3$, 500 MHz) 4.02/1.71–1.61 (m, H-12/H-13$_{ax}$), 4.02/1.32–1.26 (w, H-12/H-13$_{eq}$), 2.79–2.69/2.44 (s, H-11/H-1), 2.79–2.69/1.78–1.73 (m, H-9/H-10), 2.79–2.69/1.71–1.61 (m, H-9/H-10 and H-11/H10), 2.53–2.46/2.07–1.99 (m, H-14/H-15$_{ax}$), 2.53–2.46/1.71–1.61 (m, H-14/H-13$_{eq}$), 2.53–2.46/1.32–1.26 (m, H-14/H-13$_{ax}$), 2.53–2.46/0.90 (s, H-14/H-16), 2.44/2.07–1.99 (m, H-1/H-15$_{ax}$), 2.07–1.99/1.71–1.61 (w, H-15$_{ax}$/H-15$_{eq}$), 1.78–1.73/1.71–1.61 (m, H-10$_{ax}$/H-10$_{eq}$), 1.71–1.61/1.32–1.26 (s, H-13$_{eq}$/H-13$_{ax}$); 2D $^1$H–$^1$H NOESY NMR (CDCl$_3$, 500 MHz) 2.79–2.69/2.44 (s, H-11$_{ax}$/H-1$_{ax}$), 2.79–2.69/2.07–1.99 (w, H-11$_{ax}$/H-15$_{ax}$), 2.79–2.69/1.78–1.73 (w, H-10/H-9), 2.44/2.07–1.99 (w, H-1$_{ax}$/H-15$_{ax}$), 1.78–1.73/1.32–1.26 (m, H-13$_{ax}$/H-13$_{eq}$); IR (film) $\nu_{\text{max}}$ 2955, 2930, 2857, 1696, 1461, 1254, 1113, 1061, 910, 836, 735 cm$^{-1}$, HRMS (FAB) $m/z$ 359.2405 (MH$^+$, C$_{22}$H$_{35}$O$_2$Si requires 359.2406).
5.3 References


5.4 Selected NMR Spectra

57
(300 MHz, CDCl₃)
57
(75 MHz, CDCl₃)
58a
(300 MHz, CDCl₃)
$58a$

$(75 \text{ MHz, CDCl}_3)$
58b
(300 MHz, CDCl₃)
OTBDPS

OPMB

$58b$

(75 MHz, CDCl$_3$)
58c
(300 MHz, CDCl₃)
OTIPS

OPMB

58c

(75 MHz, CDCl₃)
OTBS

59a

(300 MHz, CDCl₃)
59a
(75 MHz, CDCl₃)
59b (300 MHz, CDCl₃)
$\text{OTBDPS}$

$\text{59b}$

$(75 \text{ MHz, CDCl}_3)$
59c
(300 MHz, CDCl₃)
59c
(75 MHz, CDCl₃)
55a
(300 MHz, CDCl$_3$)
55a
(75 MHz, CDCl₃)
OTBDPS

55b
(300 MHz, CDCl₃)
55c
(300 MHz, CDCl₃)
55c
(75 MHz, CDCl₃)
OTBS

65

(300 MHz, CDCl₃)
65
(75 MHz, CDCl₃)
$\text{EtO}_2\text{C} - \text{O} - \text{O} - \text{EtCO}_2\text{Et}$

67

(300 MHz, CDCl$_3$)
EtO₂C\[\text{O}\]O\[\text{O}\]CO₂Et

67

(75 MHz, CDCl₃)
PMBO\textsuperscript{68}\textsuperscript{OPMB}

(300 MHz, CDCl\textsubscript{3})
PMBO\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array}\text{OPMB}
\begin{array}{c}
\text{68}
\end{array}
(75 \text{ MHz, CDCl}_3)
PMBO\textsubscript{4}O\textsubscript{2}OPMB

$69$

$(300 \text{ MHz}, \text{CDCl}_3)$
PMBO\(\text{C} \equiv \text{O}\)PMB

69

(75 MHz, CDCl\(_3\))
(300 MHz, CDCl₃)
OTBS

72

(75 MHz, CDCl₃)
OTBS
\begin{center}
\includegraphics[width=\textwidth]{structure.png}
\end{center}

\textbf{73}

(300 MHz, CDCl$_3$)
73
(75 MHz, CDCl₃)
OTBS

74

CON(OMe)Me

(300 MHz, CDCl₃)
OTBS

CON(OMe)Me

74

(75 MHz, CDCl₃)
(300 MHz, CDCl₃)
76
(300 MHz, CDCl$_3$)
syn-23
(500 MHz, CDCl₃)
syn-23
(125 MHz, CDCl₃)
24
(500 MHz, CDCl₃)
24

(125 MHz, CDCl₃)
2a
(500 MHz, COSY, CDCl₃)

Relax. Delay 0.400 sec
Cost 90-90
Acq. time 0.223 sec
Width 4593.7 Hz
3D Width 4593.7 Hz
8 repetitions
256 increments

Acquire 809.911373 MHz
DATA PROCESSING
Sine bell 0.111 sec
FI DATA PROCESSING
Sine bell 0.056 sec
FT size 1024 x 1024
Total time 32 min, 35 sec
24
(500 MHz, NOESY, CDCl₃)

Relax. delay 1.000 sec
Mixing 0.400 sec
Acq. time 0.218 sec
Width 4299.5 Hz
2D Width 4299.5 Hz
8 repetitions
2 x 256 increments

Observe H1, 499.9135729 MHz

Data Processing
Line broadening 0.2 Hz
F1 Data Processing
Line broadening 0.2 Hz
FT size 2048 x 1024
Total time 1 hr, 29 min, 27 sec